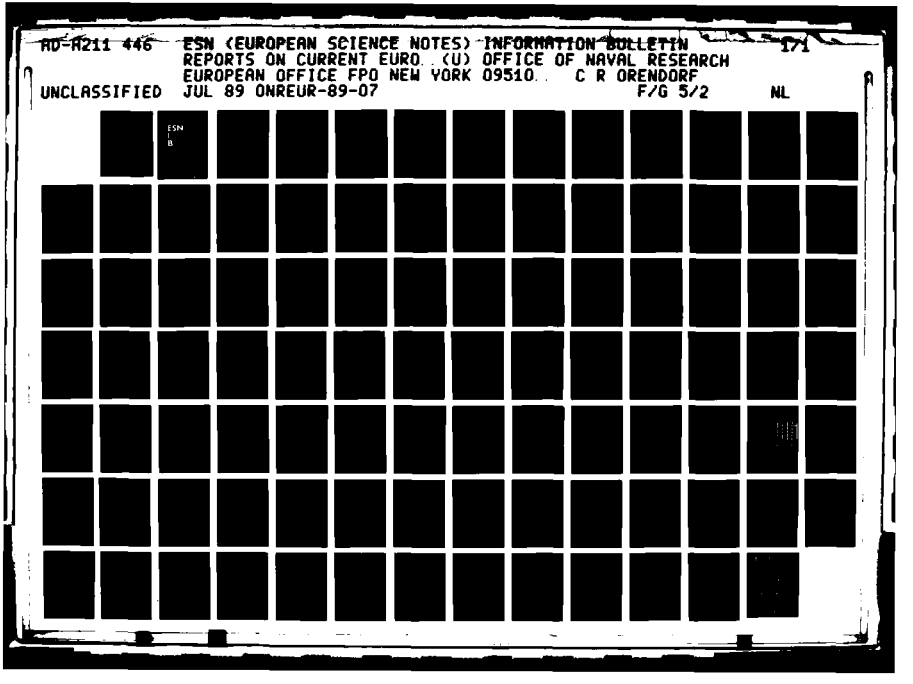
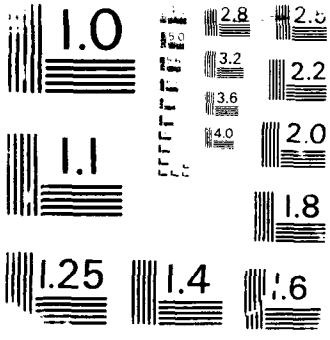

AD-A211 446 ESN (EUROPEAN SCIENCE NOTES) INFORMATION BULLETIN 1/1
REPORTS ON CURRENT EURO.. (U) OFFICE OF NAVAL RESEARCH
EUROPEAN OFFICE FPO NEW YORK 09510.. C R ORENDORF
UNCLASSIFIED JUL 89 ONREUR-89-07 F/G 5/2 NL
ESN
1
B


1.0
1.1
1.25
1.4
1.6
2.8
3.2
3.6
4.0
2.2
2.0
1.8

Office of Naval Research
European Office

89-07

ESN INFORMATION BULLETIN

European Science Notes Information Bulletin
Reports on Current
European/Middle Eastern Science

REPORT DOCUMENTATION PAGE

1a REPORT SECURITY CLASSIFICATION UNCLASSIFIED	1b RESTRICTIVE MARKINGS
2a SECURITY CLASSIFICATION AUTHORITY	3 DISTRIBUTION AVAILABILITY OF REPORT Approved for public release; distribution unlimited
2b DECLASSIFICATION / DOWNGRADING SCHEDULE	
4 PERFORMING ORGANIZATION REPORT NUMBER(S) 89-07	5 MONITORING ORGANIZATION REPORT NUMBER(S)
6a NAME OF PERFORMING ORGANIZATION Office of Naval Research European Office 6b OFFICE SYMBOL (If applicable) ONREUR	7a NAME OF MONITORING ORGANIZATION
6c ADDRESS (City, State, and ZIP Code) Box 39 FPO, NY 09510-0700	7b ADDRESS (City, State, and ZIP Code)
8a NAME OF FUNDING/SPONSORING ORGANIZATION 8b OFFICE SYMBOL (If applicable)	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c ADDRESS (City, State, and ZIP Code)	10 SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO / PROJECT NO / TASK NO / WORK UNIT ACCESSION NO

11 TITLE (Include Security Classification)

European Science Notes Information Bulletin – (UNCLASSIFIED)

12 PERSONAL AUTHOR(S)
Ms. Connie R. Orendorf, Editor

13a TYPE OF REPORT	13b TIME COVERED FROM ____ TO ____	14 DATE OF REPORT (Year, Month, Day)	15 PAGE COUNT
Multidiscipline		July 1989	88

16 SUPPLEMENTARY NOTATION

17 COSATI CODES			18 SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

The European Science Notes Information Bulletin (ESNIB) is a compilation of reports on recent developments in European science of specific interest to the U.S. research and development community, and is issued in support of the mission of the Office of Naval Research European Office. It is not intended to be part of the scientific literature. The value of the ESNIB to Americans is to call attention to current activity in European science and technology and to identify the institutions and people responsible for these efforts. The ESNIB authors are primarily ONREUR staff members; other reports are prepared by or in cooperation with staff members of the USAF European Office of Aerospace Research and Development or the U.S. Army Research, Development and Standardization Group. Scientists from the U.S. who are traveling in Europe may also be invited to submit reports.

20 DISTRIBUTION/AVAILABILITY OF ABSTRACT	21 ABSTRACT SECURITY CLASSIFICATION	
☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	UNCLASSIFIED	
22a NAME OF RESPONSIBLE INDIVIDUAL Ms. Connie R. Orendorf	22b TELEPHONE (Include Area Code) (44-1) 409-4340	22c OFFICE SYMBOL 310

DD FORM 1473, 84 MAR 83 APR edition may be used until exhausted
All other editions are obsolete

☆ U.S. Government Printing Office 1986—607-044

ESN INFORMATION BULLETIN

89-07

This publication is approved for official dissemination of technical and scientific information of interest to the Defense research community and the scientific community at large.

Commanding Officer ..... CAPT Victor L. Pesce, USN
Scientific Director ..... James E. Andrews
Editor ..... Ms. Connie R. Orendorf

BIOTECHNOLOGY

FLUID MECHANICS

MATERIALS SCIENCE

The focus of this conference was on practical presentations and discussions of the conference theme. That theme was the materials and mechanics technologies that support the design and safe operation of pressure vessels and piping for service where large amounts of hydrogen are present at high temperatures.

MATHEMATICS

CERFACS conducts research for optimum use of high performance computers with parallel architecture, and provides advanced training in scientific computation to European researchers, scientists, and engineers. The author discusses work underway in parallel algorithms, real flows, instabilities and turbulence, visualization and post processing.

The organization and relationships, along with a commentary on their research concerns, are discussed in this broad-based view of Trondheim University and SINTEF. The conclusion is that the working relationship between elements of the university, SINTEF, and the closely aligned companies, as revealed by the article, is an enviable one.

Focus is on Norway's IBM Bergen Scientific Centers and Chr. Michelson Institute. The former is a purely information development facility; the latter combines R&D with ability to put products on the market.

The author discusses this laboratory's work in developing mathematical software for the programming language Ada. Their work, he says, in developing Ada programs for numerical computation--their efforts in defining guidelines for such projects--will have a longlasting a[illegible]beneficial effect.

PHYSICS

The Physikalische Technische Bundanstalt (PTB) was the forerunner of the National Physical Laboratory, U.K., and the National Institute of Science and Technology, U.S. The author discusses the PTB's history and current resource.

The author discusses Raman spectroscopy history and the impact that spectroscopy has had in Chemistry, Materials Science, Physics, and Biology.

STRUCTURAL DYNAMICS

The Group for Aeronautical Research and Technology in Europe has formed a subgroup to address problems related to the refinement of structural dynamics models. In this article objectives, work outline, and progress are discussed.

SUPERCONDUCTIVITY

Both classical and high temperature superconductor research at the University of Göttingen's Institutes for Low Temperatures and Metal Physics is reviewed. Classical superconductors studied are primarily Nb_3Al and the A15's. Charge carriers and Fe substitutions are studied in the high T_c superconductors. Related research is with compound semiconductors and amorphous metals.

TELECOMMUNICATIONS

The proposed change in the Deutsche Bundespost of the telecommunications organization is outlined in this article. Also, future research is discussed.

NEWS, NOTES, AND ABSTRACTS

BIOTECHNOLOGY

ACHEMA' 88--Biotechnology Conference, Frankfurt, West Germany

by Claire E. Zomzely-Neurath. Dr. Zomzeley-Neurath is the Liaison Scientist for Biochemistry, Neurosciences and Molecular Biology in Europe and the Middle East for the Office of Naval Research European Office. She is on leave until July 1989 from her position as Director of Research, the Queen's Medical Center, Honolulu, Hawaii, and Professor of Biochemistry, University of Hawaii School of Medicine.

Introduction

ACHEMA '88, an international meeting on chemical engineering and biotechnology, held every 3 years, was held at the exhibition and conference center, Frankfurt, West Germany, under the auspices of DECHEMA (DeutchesGesellschaft fur Chemische Apparatwesen, Chemische Technik und Biotechnologie). Large attendance--6,000 participants from 69 countries--was because of extensive equipment and products exhibits, 3,000 totaling exhibits with 300 dealing with biotechnology. Thus, most participants were primarily interested in the exhibitions reflected by industrial attendees.

The scientific sessions dealt with:

- Biotechnology
- Foodstuffs, apparatus, equipment, processes
- New processes in chemical engineering
- Pharmaceutical technology
- Electrochemical Processes
- Waste gas, effluent, waste recycling
- New processes in chemical engineering
- Advances and developments in thermal process engineering
- Advances and developments in mechanical process engineering
- Design developments in the construction of equipment, machinery, and plant
- Use of computers in chemical engineering
- Packaging, storage, and transport
- Reaction engineering
- Safety engineering in the chemical industry
- Materials for chemical engineering
- Measurement and analysis techniques

This report will cover only the sessions on biotechnology that encompassed a large amount of material. Selected summaries will be covered focusing on research by European scientists.

Fermentation and Biotransformation

W. Hartmeier, Department of Technical Biochemistry, Hohenheim University, Stuttgart, West Germany, presented a report on lactic acid production by immobilized and extractive systems. This work was a collaborative study with scientists from the Institute of Microbiology, Aachen University, West Germany. The aim was to install continuous operation in lactic acid production using matrix-free immobilizates and to apply native cells in an extractive bioconversion process.

Hartmeier and coworkers used a newly isolated flocculent strain of *Lactobacillus* species without inert carrier material in a continuously operated tower reactor. This process led to the production of the L(+)-isomer of lactic acid.

P. Czermak, ENKA AG, Research Institute, Obernburg, West Germany, discussed the use of dialysis-membrane reactors for the enzymatic separation of biotechnological products in which he worked with W. Bauer, Fraunhofer Institute for Food Technology, Munich, West Germany. Use of dialysis-membrane reactors represents an advanced development since substrate solution and enzyme solution are separated by the membrane in a steriie way, and diffusion can achieve high mass transfer and conversion rates. This is an essential advantage when dealing with heterogeneous substrates that contain a large number of ingredients such as milk and whey. An advantage with other substrates is where it is not desirable to leave the enzyme in the product. Using the dialysis-membrane reactor eliminates removal and recovery of enzymes, which in some cases could be difficult and costly.

On one hand, suitability of the dialysis-membrane reactor for enzymatically catalyzed processes is explained by the fact that with dialysis the mass transfer of substrate and product is effected by diffusion through the membrane, thus making possible a sterile compartmentation of the enzyme. On the other hand, the membrane used for molecules up to a molecular weight of approximately 5000 Dalton has a high permeability, thus ensuring a high efficiency of the mass transfer.

Czermak reported on the steam-sterilizable dialysis-membrane reactor as well as a method for enzymatically catalyzed processes. The functional efficiency of the continuous process was demonstrated by the results of the hydrolysis of lactose from milk on a laboratory and pilot plant scale.

R. England, School of Chemical Engineering, University of Bath, U.K., reported on the development of a process for N-demethylation of drug intermediates by microbial means, a joint project with C.J. Sope . School of Pharmacy and Pharmacology, Bath. Many drug molecules possess N-alkyl functions, usually in saturated structures or in alkylamine chains. Variations in the N-alkyl function often produces substantial alterations in pharmacological activity. In view of this, it is often required to replace pre-existing N-alkyl function (usually methyl) with different substrates in order to facilitate more selective or more potent therapeutic agents. This is usually achieved by N-dealklyating the parent drug molecule to produce a primary or secondary base intermediate from which a variety of N-substituents may be prepared by alkylation, acylation, or arylation.

Although N-dealkylation can be carried out by chemical methods, there are problems such as variable product yields and toxicity of some of the reagents used. Therefore, England and colleagues were interested in replacing conventional chemical methods of N-dealkylating drug intermediates by biotransformations. They found that the filamentous fungi *Cunninghamella baineri* possessed a wide substrate specificity in its N-dealkylation activity.

Scaleup of the bioreaction from shake flask to a 5-liter airlift fermenter was achieved by England and coworkers using the N-dealkylation of the opiate codeine (as codeine phosphate) to norcodeine as the test system. Alginate gel immobilization of the *Cunninghamella* and subsequent culture to obtain the desired pellet growth form was investigated. Because of the presence of chelating agents in the fermentation media, it was found necessary to develop a method for the stabilization of the alginate gel against attack by these compounds. A polyethyleneimine (PEI)-activated alginate gel was developed for the immobilization of the microorganism and the gel was found to be stable in the presence of solutions containing up to 0.25 molar phosphate. Successful culture of the *Cunninghamella* in the pelleted form was achieved by this method.

Cell Culture Technology

E. Thalmann, Chemap AG, Volketswil, Switzerland, discussed the kinetics of BHK cells in a bioreactor with an aeration system through a mesh (CHEMCELL). The increased interest in large scale production of biologically active molecules; e.g., monoclonal antibodies (Mabs), hormones, proteins, and enzymes has stimulated a rapid development of different methods to cultivate eukaryotic cells. Further progress in modern biotechnology is expected not only from the selection of more productive cell lines and more efficient cultivation techniques, but also from the improvement in new bioreactor design and operation, which guarantees increased productivity per unit volume and reduces the downstream processing. The most important factors for a new reactor design in the future will be the sterility, energy and mass transfer, shear stress, and scaleability. The provision of an adequate oxygen supply to large scale reactors is the most critical barrier to scale up. If oxygen is limited in a small degree, the result is inhibition of cell density and cellular efficiency in the production of the desired biomolecules. In addition, when methodologies are used that allow high cell densities and high metabolically active cells, the oxygen transfer becomes more important and, at the same time, more difficult. Since direct sparging of air into the cell-containing medium causes problems; e.g., shear forces and foaming, efficiently bubble-free separation must be obtained.

Thalmann then presented information about the CHEMCELL system a new product from his company, Chemap AG. This system is suitable for bubble-free aeration as well as for microcarrier-anchored cells separated from the harvested medium when running in a continuous perfusion mode. The efficiency of the CHEMCELL system regarding aeration and cell retention was demonstrated by the growth kinetics of BHK 21-cells in batch and perfusion mode.

O.L. Goldring, Fermentech Ltd, Heriot-Watt University Campus, Edinburgh, U.K., spoke about parameters affecting Mab purification using Protein A affinity chromatography. Protein A is widely accepted as being a suitable ligand for purifying IgG_{2a} and IgG_{2b} mouse monoclonals as well as mouse IgG_1 and IgG_3 subclasses.

Goldring and coworkers developed a computer controlled system for the laboratory scale Mab purification from either tissue culture medium or mouse ascites fluid. The computer receives and interprets an incoming data stream (time/pH values) from a Corning Model 150 pH-ion meter with attached flow cell, and LKB Uvicord III Spectrophotometer (OD 280 value). The system is auto-

mated by an interfaced console, controlling a series of solenoid valves (Lee Products Ltd), a peristaltic pump (LKB), a gradient mixer (Pharmacia), and a fraction collector (LKB). This allows rigid control over sample loading, column washing, and subsequent pH gradient elution of purified Mab from a Protein A Sepaharose column (Fermentech Ltd). Sample loading can be controlled by volume or time, and can range from milliliter to liter quantities. Column washing, subsequent to the loading cycle, can be carried out until the eluate reaches a predetermined low OD 280 value; e.g., 0.01. At this stage an operator can set a washing time extension option. Purified Mab is recovered from the Protein A Sepharose column using a pH gradient (or by step elution). Using this approach, Goldring and coworkers examined several variations associated with the purification technique (as commonly practiced by individuals who purify mouse monoclonals.)

Biocatalysts

K.D. Kulbe, Fraunhofer Institute for Separation and Bioprocess Techniques, Stuttgart, West Germany, reported on the enzymatic transformation of carbohydrates by continuous redox and phosphate transfer processes. Renewable carbohydrates can serve as substrates for a large number of chemical, fermentative, and enzymatic production processes. At present, only hydrolysis and isomerization reactions are used for enzymatic carbohydrate conversions on an industrial scale. Many more carbohydrate derivatives with industrial potential; e.g., nondiabetic sweetener or mild acids for foods, vitamins, surfactants, cryoprotectants, or pharmaceuticals may be produced by the development of coenzyme-dependent dehydrogenase and reductase catalyzed hydrogen transfer reactions as well as ATP-dependent kinase or Pi-dependent phosphorylase catalyzed phosphate transfer reactions into technical processes.

For economic reasons, the cofactors involved have to be regenerated. With nicotinamide coenzymes this can be advantageously achieved by a combination of suitable enzyme catalyzed reduction and oxidation steps with identical coenzyme specificity. The coenzyme is regenerated either in a conjugated manner, by connecting two basically independent reactions requiring the same coenzyme--NAD(P), redox dyes--in oxidized or reduced form, or inrasequentially, where the first reaction product serves as the second reaction substrate.

The feasibility of both concepts for NAD(P)H recycling in continuous operation was demonstrated by Kulbe and coworkers by enzyme catalyzed procedures that simultaneously yielded (1) manntitol (or sorbitol) and gluconic acid from fructose-glucose mixtures; (2) sorbitol and gluconic acid from glucose; and, (3) dihydroxyacetone from glycerol and a polyol from either monodisaccarides or disaccharides. L-sorbitol was prepared enzymatically from D-glucose/D-fructose via D-sorbitol using product-coupled NAD(P)H regeneration.

Further pathways comprising intrasequential cofactor regeneration are presently being studied for the synthesis of L-ascorbic acid from D-gluconic acid or D-hexuronic acids. Regarding the continuous phosphate transfer, carbohydrate conversion, depending on other adenine nucleotides; e.g., kinase catalyzed ATP requiring reactions yielding sugar phosphates, and systems for enzymatic ATP regeneration are presently being investigated in several laboratories including Kulbe's.

Using free enzymes, the cofactors (NAD, NADP, ATP) may be retained in the reactor either by charged or uncharged ultra- filtration membranes. Using uncharged ultrafiltration membranes requires that the coenzyme is tightly bound to the enzyme or that it is artificially macromolecularized. Native free coenzyme is advantageously applicable in reactors equipped with charged ultra-filtration membranes bearing the same net charge as the coenzyme under the conditions applied. In the latter case, the ionic strength in the reaction vessel should be kept low.

A. Schmid, Institute for Technical Chemistry, University of Munich, West Germany, reported on the influence of pressure on immobilized enzymes. Schmid's previous investigations concerning the influence of pressure on the hydrolysis of succinyl-L-phenylalanine-4-nitroanilide (SUPHEPA), catalyzed by chymotrypsin A which was covalently bound to Eupergit C (Rohm Pharm.) showed a pressure-induced enhancement of activity up to 116 percent at 70°C and 300 bar/l. Moreover, the temperature of denaturation of the carrier-bound enzyme increased from 65°C to 70°C at 300 bar. However, in homogeneous solution at 50°C and the same pressure the enhancement was only 43.2 percent. Searching for the reason stimulated Schmid's and coworkers' investigation of different conditions as well as studies of other enzyme/substrate systems.

In summary, Schmid and his group found that the increase in stability because of immobilization was increased more by pressure. In many cases, this improvement of the stability and the hold-up time often resulted in a more favorable technical use of biocatalysts.

Downstream Processing

U.B. Sleytr, Center for Ultrastructure Research, University of Agriculture, Vienna, Austria, discussed ultrafiltration membranes from two-dimensional protein arrays. Many eubacteria and archaebacteria possess a regularly structured crystalline layer (S-layer) as their outermost cell wall component. S-layers are composed

of a single protein or glycoprotein species. So far, S-layers with oblique (p2) square (p4) and hexagonal (p6) lattices have been identified. Depending on the type of lattice, one morphological unit is composed of two (p2), four (p4), or six (p6) subunits. Since in eubacterial S-layers the subunits are linked to each other by noncovalent bonds, they can be liberated from the underlying cell envelope layer using high concentrations of chaotropic agents or by shifting the pH. During removal of the disrupting agents, the subunits frequently reassemble into regularly structured lattices identical to those observed in intact cells.

Since S-layers represent two-dimensional protein crystals, electron microscopical and digital image processing procedures can be used for high resolution studies on the mass distribution. Sleytr and coworkers obtained information on the functional pore size by permeability studies. Both the electron microscopical evaluation procedures and permeability studies showed that S-layers work in the ultrafiltration range. Thus, ultrafiltration membranes, in which the active filtration layer is composed of coherent S-layer fragments, have been developed by Sleytr and coworkers. Such S-layer ultrafiltration membranes (SUM) made up of S-layer material from highly thermophilic *Bacillaceae* displayed rejection curves with a steep increase between molecular weights of 30,000 and 45,000. Because of surface-located free carboxyl groups originating from the acidic amino acids of the S-layer protein, SUM have a net negative charge under neutral conditions. Both the surface net charge and the hydrophobicity of the membrane can be altered by chemical modification of the carboxyl groups. Because the crystalline S-layer lattice is composed of identical subunits, it is evident that surface-located functional groups must be present on each subunit in an identical well defined position.

Carboxyl groups and hydoroxyl groups exposed on the S-layer surface were used by Sleytr and his group for the immobilization of biologically active molecules; e.g., enzymes. Electron microscopical studies showed that macromolecules were covalently attached to the S-layer lattice in the densest possible packing order. These preliminary studies clearly indicate that S-layers represents a new type of support for immobilizing macromolecules.

H. Schütte, Institute for Biotechnology Research GBF, Braunschweig, West Germany, presented a report on the mechanical disruption of microorganisms in agitated bead mills. This was a collaborative project with M.R. Kula, Institute for Enzymology, University of Düsseldorf, Jülich, West Germany. Kula was formerly at GBF and is well known for her biotechnology research. Schütte said that agitated bead mills (ABM) have established themselves for the purposes of fine size reduction and dispersion of many industrial product areas. In addition to the processing of coating and surface materials, pigments and hard metal powder suspensions, various applications in the chemical and ceramic industries and, in more recent years, biotechnology, have been established. ABM's have been used increasingly for the disruption of microorganisms for the release of intracellular proteins both in the laboratory and in production. The high mechanical stability of microorganisms and the small particle size – 1 to 5 μm – make high demands on the homogenization process. Because of this, initial investigations concentrated on the optimization of parameters; i.e., agitator speed, feed rate, and glass bead size for various organisms in order to effect an efficient disruption with the lowest possible number of passages. For example, equipment parameters, the agitator and disc geometries have only recently been investigated. Schütte and Kula had shown that the residence time distribution effects of the stirrer and energy transfer from the stirrer to the beads could be significantly improved. A tight residence time distribution was found to be essential to keep the mechanical stressing of the microorganisms constant and thereby retain the activity and functionality of the proteins without unnecessary comminution of the cell walls. The improved energy transfer and resultant higher shear rates increase the disruption capacity especially for bacteria.

Continuous processing in high speed ABM's is universally applicable to the disruption of yeasts, bacteria, plant cell cultures or mold mycelia, and even gram-positive bacteria with their high strength cell walls where other mechanical methods fail. Novel methods of online determination of cell content were applied to increase the resolution with which the disruption process could be followed. Quantitative results may be obtained by measurements of parameters such as pH or conductivity online; both these parameters may be correlated with the degree of disintegration.

Using flow injection analysis (FIA) allows the process to be followed quantitatively; approximately 60 protein concentration or enzyme activity determinations per hour may be carried out online with FIA. The particle-free sample to the flow injection analyzer is obtained by filtration through a sampling device (Biopem). Good monitoring of the disruption process is thus guaranteed and quick optimization of the agitator speed or feed rate for a particular microorganism is made possible.

A. Bomberg, DECHEMA Institute, Frankfurt, West Germany, reported on a method for cell disintegration by high turbulent liquid impingement jets. A prerequisite for the recovery of intracellular bioproducts is the disintegration of the microorganisms that have synthesized these products. Recently, Bomberg and coworkers have developed an alternative disintegration method based on the impingement of two high turbulent liquid jets of a microorganism suspension that are directed to each other. These researchers carried out parameter studies on nozzle type, relative velocity of the liquid jets, number

of passages, as well as using various types of microorganisms.

The requested pressure before the nozzles is only 25 to 30 percent of the pressure needed in high pressure homogenizers for comparable disintegration results. Disruption of *E. coli* organisms at a relative velocity of 180m/s, which corresponds to approximately 140 bar system pressure, allows a disintegration degree of 60 percent within 1 passage and 95 percent after 4 passages. Product stability studies using model enzymes showed that also after 10 or even 14 passages, product deterioration is negligible; similar results were obtained with *S. cerevisiae*.

R. England, School of Chemical Engineering, University of Bath, U.K., reported on a method he and his coworkers developed in which the selective extraction of N-demethylated products from bioreactors was carried out successfully using liquid organofunctionalized polysiloxanes.

U. Muller, Department of Technical Chemistry B, University of Dortmund, West Germany, reported on his and his group's development of an extractive fermentation process--*in situ* extraction. The *Streptomyces griseus* producing cyclohexanoide was used as a test system for the extractive fermentation. Muller discussed also product-inhibited formation of the antibiotic cyclohexamide as well--the basis for selecting a suitable solvent.

M. Papamichael, Institute for Biotechnology Research (GBF), Braunschweig, West Germany, discussed the design of economically attractive aqueous two-phase protein extraction processes. Aqueous two-phase extraction should become a well established technology for the downstream processing of proteins. The method is rather expensive compared to other established techniques. However, by appropriate process design, the costs can be drastically reduced. Important factors regarding the economics as presented by Papamichael are

- The selection of the phase system--type and molecular weight of the polymer(s)--type of salt--e.g., a polyethylene glycol (PEG) 4000/MgSO4-based system is much cheaper than a PEG 1500/potassium phosphate system
- Biomass content in the phase system (this should be at least 20 percent, but preferably higher)
- Recycling of the phase-forming chemicals.

Papamichael discussed the effect of the above parameters on the economic situation of the extraction technology and presented organizational guidelines. He also discussed new directions; e.g., continuous crosscurrent extraction and reactive extraction.

G. Ganetsos, Department of Chemical Engineering and Applied Chemistry, Aston University, Birmingham, U.K., reported on studies on the application of chromatographic systems as combined biochemical reactor-separators. This type of operation improves the yield in the biosynthesis of macromolecules such as dextran. Such systems have been scaled up to 5.4 cm column diameter and the effect of construction and voidage materials were also investigated. This method represents an important new application of chromatographic reactor-separators in the biochemical field. Because of the simultaneous removal of acceptor byproducts, macromolecules of better yield can be produced. The chromatographic biosynthesis of dextran not only produced increased high molecular weight dextran, but also provided a new source of high purity fructose.

H. Voss, Biotechnikum, Martin Luther University, Halle, East Germany (GDR), reported on a special technique for extractive fermentation using immobilized microorganisms. Voss and his coworkers also developed a mathematical model that allows the prediction of optimum process parameters and suitable equipment design.

Bioprocess Control

F. Valedo, Department of Chemical Engineering, University Autonoma, Bellaterra (Barcelona), Spain, reported on the development of flow injection analysis (FIA) equipment for online monitoring for glucose analysis in fermentation processes. Valero discussed the potentially using of this method to identify disturbances to the system.

K. Futschik, Bioelectricity and Magnetism Division, University of Technology, Vienna, Austria, reported on a new impedance method to automatically register microorganism growth. Electrical impedance measurements are being used increasingly to detect and monitor microorganism growth processes. In comparison, for example, to the plate count method, the main advantages of this technique are automatic measuring process and evaluation. The measuring system based on a new impedance method allows simultaneous monitoring of up to 200 microorganism cultures (bacteria), yeast, and algae cultures.

Microorganisms may be tested by impedance methods by cultivation in nutritious liquid media; thereby, several growth parameters can be varied widely. For a long time, ionic changes of the culture medium because of microbial metabolism were utilized for the registration of microbial growth. As a result of these ionic changes, the measured impedance Z_s of the culture medium is changed. The new system offers the possibility for a separate registration of the changes of the ionic double layer at the measuring electrodes, which is responsible for the so-called electrode impedance Z_s. This method offers two advantages for microbial testing: (1) disturbances caused by the electrode system can be eliminated and (2) Z_s represents a second information for the growth process. The time period T was determined for measuring microbial con-

centrations by the impedance method. The initial concentration of microorganisms was inversely proportional to T. Automatic determinations of the initial microorganism concentration were made possible by calibration curves.

Important areas of application are tests of antibiotics or inhibitory substances. Futschik and his group added different inhibitory substances to the microorganism cultures and microorganism growth was recorded during the growth process. Another field of application is optimizing culture media or culture conditions. As an example, they studied the effects of nutrient additions – yeast extract – at two different concentrations compared to a pure nutrient broth. The influence of temperature, stirring or aerating, and aerobic or anaerobic growth conditions can also be studied.

D. Schneidt, Heinrich Frings Gmbh & Co., Bonn, West Germany, discussed the results of experiments for determination of the time that is required for total mixing of aerobic fermenters and chemical reactors for gas-liquid reactions. During these experiments, it became obvious that long time periods might be required to obtain even concentrations of indicator substances all over the vessel. Even if the radial mixing were quite fast, it took much more time for the equilibration of vertical concentration differences. These problems could be avoided by using a simple structure inside the vessel. This structure allows a loop for the liquid phase, in this way equalizing differences in concentrations very quickly.

With this loop-reactor, the mass transfer coefficient was enhanced and this allowed for better use of necessary gas compounds and higher growth rates for microorganisms or chemical reactions. However, this is valid only for processes that are limited by adding gaseous or liquid additives. In the same way, local differences will be equalized, which in chemical reactions could be advantageous for the composition of the product, if there are competitive reactions. For fermentations, it is possible to drastically reduce the amount of antifoam agent.

Bioreactors

W. Kung, Bioprocess Technology Division, Institute of Biotechnology, Technical University of Graz, Austria, dealt with the topic of the horizontal bioreactor. The horizontal tubular bioreactor is a further development of the Tubular Plug Flow Reactor conceived at the Graz Technical University. The objective of Kung's and colleagues' work was to produce a plug flow bioreactor that is as ideal as possible for biotechnology purposes on laboratory and pilot-plant scale. Special consideration was given to commercial aspects with respect to potential use in aerobic and anaerobic biological systems. Using plug flow reactors in biotechnology was previously restricted to using continuous sterilization, in waste water purification, and, to some extent, in enzyme technology.

From the aspect of flow technology, plug flow is in a position to have a stimulating effect on continuous culture techniques in the industrial sphere, in which the important points of primary interest are: (1) avoiding substrate inhibition; (2) utilizing residual substrates; (3) continuously producing of products that are not growth-associated; (4) operating with flock or fixed-carrier cells; and (5) biological producing of systems that require gradients or pulses.

Kung presented the first experimental results and experience with the new design on a laboratory and pilot-plant scale using the example of anaerobic ethanol production with *Zymomonas mobilis*. The advantages of a tubular reactor compared with a continuous stirred vessel are:

- High conversion at optimum productivity is possible for reactions of orders higher than one
- Inhibition avoidance of the substrate is possible
- Gradient and pulse inputs are possible
- Continuous product formation is possible in the stationary growth phase
- Sterility without recycling is easy to achieve.

E. Liefke, Chemical Technology Division, University of Dortmund, West Germany, reported on the cultivation of aerobic microorganisms under increased pressure in a specially designed pressure-fermenter. In aerobic fermentation processes, increased total or partial pressures are used to enhance oxygen transfer. However, because of the size of industrial fermenters, higher pressures are a consequence of liquid height. Up to now, the influence of increased oxygen pressure has been neglected in scale-up, probably because suitable experimental equipment was not available on laboratory scale. Therefore, Liefke and coworkers developed a special pressure-fermenter for the cultivation of aerobic microorganisms under increased total and partial pressure. This airlift loop-fermenter can be operated at pressures up to 10 bar and shows favorable mixing behavior with similar efficiency as in stirred tank fermenters. Since it has no moveable parts, continuous cultivation under sterile conditions is possible for weeks with low risk of contamination. The fermenter can be run with nutrient media of low-to-middle viscosity, even with a high content of solids as used in industrial processes for antibiotics production.

Investigations on the influence of pressure on the production of biomass and secondary metabolites demonstrated inhibitory effects in all cultures studied, and in some cases, with total inhibition of growth. However, an enzyme blockade by oxygen was identified as the cause for these effects. By specifically applying increased total or partial pressure, positive effects on growth and pro-

duct formation could be obtained as shown with *Methylomonas Clara* and *Streptom; ..es Rimosus*.

Conclusion

The biotechnology sessions at Achema'88, the international conference on chemical engineering and biotechnology covered many aspects of biotechnology; e.g., fermentation process and biotransformation; cell culture technology; downstream processing; bioprocess modeling; and bioreactors. Scientists from West Germany, dominated the presentations although there were some excellent talks by U.S. scientists. Since ONREUR's emphasis is on research by European scientists, the latter are not included in this report. The quality of the research presented was first rate.

Thermodynamics Applied to Biological Systems--International Symposium

by Claire E. Zomzely-Neurath.

Introduction

The conference entitled *International Symposium on Thermodynamics Applied to Biological Systems* took place in Santa Margherita Ligure (suburb of Genoa), Italy. Professor Giovanni Rialdi, University of Genoa, assisted by an international advisory committee organized this small, focused meeting. Professor Rialdi and his advisory committee will hold a symposium on the same topic every 2 to 3 years in different European countries. ONREUR contributed to this timely and interesting conference.

Of the 153 participants in the scientific program, 47 were from the U.S., and 81 from 9 Western European countries and the U.K. Nine participants were from the U.S.S.R. including Eastern European countries and seven from countries outside of Europe and the U.S. Thus, the group had an excellent and balanced international makeup.

The scientific program was intense and occupied 4 1/2 days with two evening scientific sessions. The sessions consisted of two major lectures per day, a number of shorter presentations, poster sessions, and moderated plenary discussions. The symposium presentations were arranged according to the type of problems addressed, irrespective of methods employed or materials studied. This was extremely useful since it focused attention on the biological problems to be addressed rather than rigid methodological orientation. The proceedings of this conference will not be published.

A lot of information was presented at this conference so I summarized selected reports by European scientists here. Although there were several excellent presentations by U.S. scientists, I omitted them because of the space limitations and because the primary objective here is to feature European scientists' research.

Thermodynamic Stability and Specific Amino Acid Alerations in Proteins

A.A. Makarov, Institute of Molecular Biology, U.S.S.R. Academy of Sciences, Moscow, U.S.S.R., presented an interesting report on the subject of thermodynamics of protein crystals. A great part of proteins function in condensed state, so the problem is to analyze conformational dynamics variations at contacts. Makarov and colleagues have studied thermodynamics of protein crystals as a highly ordered model of the condensed state. For nine proteins differing in their molecular weights and complexity of spatial structure crystals do not melt and destruction of the crystal lattice is a result of protein globule thermal denaturation within the crystal. Denaturation transition in pepsin and trypsin crystals is a phase transition of the first order. The equilibrium state of water in protein crystals was shown for a wide temperature range.

Makarov and his group also analyzed the peculiarities of domain structure of proteins in the crystal state. Upon crystallization of pepsin, the dielectric constant of the system was altered, thereby demonstrating the diminishing of a total amount of water molecules strongly bound by protein. Equilibrium temperatures of protein denaturation in crystal and in solution coincide. The peculiarities of the crystal state were exhibited in increased thermal transition cooperativity and the system's relaxation time. Makorov concluded that based on the variation of protein packing, it is possible to control the degree of synchronization of cell processes. The data obtained

enabled Makorov and his colleagues to explain a biological phenomenon of correlation between cell proteins thermostability, cell thermostability, and species environment temperature.

P.L. Mateo, Department of Chemical Physics, Faculty of Science, University of Granada, Spain, spoke about differential scanning calorimetry (DSC) studies of irreversible thermal denaturation of proteins and the application of the scan-rate effect. Thermodynamic analysis of DSC calorimetric traces because of protein unfolding relies on the assumption that chemical equilibrium exists throughout the process. It is not clear, according to Mateo, whether or not equilibrium thermodynamics can be applied to calorimetrically irreversible transitions--no heat effect in the reheating of the sample. The scan-rate effect on the calorimetric traces may be used to ascertain the equilibrium character of the traces. Mateo provided several examples in which the shape of the traces, as well as the effects of the scan-rate on them, could be explained on the basis of a two-state kinetic model. According to this model, the conversion of the native state to an irreversibly denatured one (aggregated, for instance) is determined by a first order kinetic constant, that changes with temperature according to the Arrhenius equation. In these cases, no thermodynamic information, other than enthalpy changes, can be derived from the traces.

A more general situation would be the coexistence of several macrostates--conformations--of the protein in equilibrium with each other, with a final irreversibly denatured state arrived at by rate-limited processes. Mateo and his group are now developing methods of analyzing this kind of transition, based on the scan-effect on the traces. Mateo thinks that this approach might allow them to obtain and characterize the hypothetical equilibrium transitions that would be observed if the irreversible processes did not take place, as well as kinetic information about these processes.

An informative report on thermal denaturation of ribonucleases from different sources was presented by G. Barone, Department of Chemistry, University of Naples, Italy. The studies were in collaboration with A. Di Donato, Department of Organic and Biological Chemistry. As part of a program on the thermal stability of homologous proteins from different sources, Barone and his colleagues are studying, calorimetrically, the thermal denaturation of bovine pancreatic ribonuclease (RNAse) A and RNAse BS. The RNAse BS is a dimeric protein, whose two subunits are covalently linked by a pair of consecutive interchain disulfide bridges. The molecular weight is about twice that of the monomeric enzyme, the two subunits being chemically identical. Structural studies have shown that the two subunits exchange the $-NH_2$ terminal peptide.

The calorimetric data confirm that the denaturation process is really, in this case, a two-state transition. The T_d at pH = 5.0 is the same (61°C) for both the enzymes, but the values of enthalpic and entropic changes for RNAse BS is much less than twice the values of the RNAse A. According to Barone, this indicates that the denaturation processes for the two enzymes are only in part comparable, probably because the denatured state of the dimeric covalent protein has fewer degrees of freedom than the two separate monomeric units.

The parameters characterizing the RNAse-3'CMP complex indicate that the adduct is more stable than the enzyme alone. Adding of urea decreases both T_d and ΔH_d, depending linearly on the concentration of this chaotropic agent. The contrary happens in the case of sugar; also in this case, the trend is proportional to the molar concentration of glucose or to the equivalent monomeric concentration in the case of its oligomers.

Biological Activity and Specific Amino Acid Alerations in Proteins

P. Sellers, Physical Chemistry 2, Chemical Center, University of Lund, Sweden, presented an informative report on protein engineering and biophysical studies of Calbindin D_{9k}. As part of a study of structure/function relationships in EF-hand calcium-binding proteins, Sellers and his coworkers are investigating bovine Calbindin D_{9k} using a combination of biophysical methods and site-directed mutagenesis. Calbindin has two calcium-binding sites, one--the C-terminal--a typical EF-hand, and two--the N-terminal--the *pseudo EF-hand* in which the calcium ligands are mostly peptide carbonyls. Sellers and his group have synthesized a series of mutants, with changes concentrated primarily in and around the N-terminal site.

These investigators determined macroscopic calcium-binding constants using fluorescence spectroscopy and different chelators or from measurements with a calcium-selective electrode. Derived free energies of binding were combined with calorimetrically determined enthalpy values to obtain the entropy changes of calcium-binding. These were strongly positive in all cases.

Thermal denaturation studies using circular dichroism showed that the wild-type protein and the mutants studied so far are unusually stable, with denaturation of the calcium-free proteins occurring at temperatures above 80° to 90°C.

The X-ray structure of calbindin D_{9k} revealed a cluster of negatively charged amino acid side chains on the protein surface around the Ca^{2+}-sites. Sellers and his group studied the effects of substituting Glu 17, Glu 26 and Asp 19 by Gln and Asn, respectively, and have constructed all possible single, double, and triple mutants. It seems that the average contribution of each charge to ΔG_{tot} for Ca^{2+}-binding is -7kJ/mole^{-1}. Sellers discussed

the effect of neutralization of charges on the positive cooperativity of Ca^{2+}-binding as well as the enthalpic and entropic contributions to the binding energy.

J.F. Hansen, Novo Research Institute, Bagsvaerd, Denmark, spoke about enthalpy of Zn^{2+}-binding to human insulin analogue B13Gln and the influence of phenol, the entropy change and its relation to the protein interface. Zinc-free insulin (B13Glu) and the insulin analogue (B13Gln) associate at neutral pH. Molecular weight measurements (osmometric pressure at 1.5 mM insulin monomer) give 31 kilodaltons (kDa) for zinc-free insulin and 36 kDa for the analogue B13Gln and human insulin with phenol (2mg/ml). Adding 1 and 2 Zn^{2+} per hexamer gives 36 kDa for both insulins; i.e., hexamer – theoretical value of hexamer: 34, 97 kDa.

Hansen showed a figure of the hexameric arrangement of the six monomers with two identical Zn^{2+} binding sites formed by B10 histidine. In the human insulin, B13Glu is situated in a circular configuration in the center of the hexamer. The Zn^{2+} binding sites have no near contact with the B13 Glu.

Hansen presented calorimetric data that show a significant difference of Zn^{2+} binding enthalpy between the two insulin analogues and between the two binding sites within the analogue.

In human insulin with and without phenol, binding of the first Zn^{2+} per hexamer is strongly endothermic. In the insulin analogue B13 Gln, a less endothermic value is obtained. The binding enthalpy of the second Zn^{2+} in both analogues was comparable to free histidine.

If the two histidine binding sites are considered to be identical, then the endothermic enthalpy change of the first binding is mainly because of protein interactions of entropic origin and not because of the Zn^{2+}-histidine interaction. According to Hansen, the more unfavorable ΔH from the first Zn^{2+} to human insulin compared to analogue B13Gln may be caused by charge repulsion from B13 Glu.

Titration in steps of 1/3 Zn^{2+} per hexamer revealed a remarkable effect of phenol in human insulin. Without phenol, H is decreasing, going from endothermic to exothermic values, while in phenol the first five steps are of the same endothermic size, and the remaining steps are exothermic. The total ΔH with and without phenol is nearly equal.

The most probable exp'anation of the entropy producing process is changes in binding and structure of water molecules around the interacting amino acid residues in the interface. According to Hansen, the influence of phenol is presumably caused by the formation of an alternative conformation in insulin found in crystals grown from phenol. Further study of other insulin analogues may clarify to what degree it is a water effect connected to hydrophobic interactions, hydrogen bonds, or ionic interactions.

N.G. Esipova, Institute of Molecular Biology, U.S.S.R. Academy of Sciences, Moscow, U.S.S.R., presented a report on the influence of electrostatic interactions on thermodynamic properties of proteins. The analysis of X-ray data show the existence of regions with high electron density in proteins; i.e., structural domains. The question arises about how specific structural properties of domains are displayed in their energy characteristics. This problem can be solved if it is known to what extent the discreteness of the polypeptide system by one of its properties; i.e., density, is followed by the discreteness of other properties. Esipova presented data on the connection between the distribution of charges and dipole moments of peptide groups in protein globules and their physical properties. The distribution of charges in ribonuclease *Bacillus intermedius* 7p, inorganic pyrophosphate, and pepsin was studied by X-ray analysis and circular dichroism. Localization of ionic pairs with respect to globular parts characteristic of different electron density was established. Esipova and coworkers showed that the regions of extreme electron density possess maximally compensated dipole moment of peptide groups. By microcalorimetry, with the change of the electrostatic surrounding, which leads to a charge distribution in a protein molecule, the dimensions and the number of cooperative regions of the globule are changed. Structural and energy domains in ribonuclease *Bacillus intermedius* 79 and pepsin were localized.

The energy domains are characterized by compensated electrostatic interactions. The number of domains with compensated dipole-dipole interaction is greater than the amount of cooperative domains. Therefore, it is necessary to distinguish the electrostatically compensated domains in globular proteins. The necessary and sufficient conditions for domains to be displayed in energetic thermodynamic spectra of proteins are the dissociation of ionic pairs and compensation of dipole-dipole interactions of peptide groups.

Molecular Recognition in Protein

M. Bolognesi, Department of Genetics and Microbiology, University of Pavia, Italy, presented information on proteinase inhibitor recognition processes and models in the trypsin/chymotrypsin family. Bolognesi said that several high resolution crystallographic investigations have contributed to understanding the mechanisms of enzymes action belonging to the serine proteinases homologous family. More recently, a comparable number of structural investigations on proteinase protein inhibitor complexes have been conducted, and the structural basis for enzyme inhibition in this family thoroughly examined. According to the generally accepted interpretation of the (static) enzyme inhibitor complexes observed in crystal structures, the following events characterize adduct for-

mation: (1) very little conformational readjustment is needed, on both sides, for productive enzyme inhibitor recognition; (2) the inhibitor reactive site is accommodated in the enzyme's active site in an orientation consistent with that expected for a scissile substrate; (3) the enzyme inhibitor contact region includes 100 to 200 van der Waals contacts; (4) part of the contacting surface, on the inhibitor side, shows a decrease in crystallographic B factors; i.e., thermal vibration, compared to the free species; and (5) the reactive site scissile peptide bond is intact (virgin inhibitor I* as opposed to I, the inhibitor with a nick at the reactive site).

If the simplified equilibrium $E + I \rightleftarrows E.I \rightleftarrows E + I^*$ is assumed to be representative for the approximately ten serine proteinases protein-inhibitor families, the inhibitor efficiency is measured by its association constant for a given enzyme. K_{assoc} is a function of K_a (the association constant for the virgin inhibitor) and is inversely related to K_{hydr} (the equilibrium constant for the I to I* hydrolysis of the inhibitor. K_a values range between 10^4 and 10^{13} (M^{-1}), according to the particular inhibitor-cognate (pro)enzyme couple (and according to the level of activation achieved in the proenzyme selected). On the other hand, K_{hydr} does not differ from unity for several inhibitors, at neutrality. Most of the structural features of the polypeptide inhibitor molecules, such as the presence of disulphides, together with those observed at the E-I contact area, are consistent with a highly specific and conserved recognition mechanism, with maximization of K_a, and with the achievement of inhibition through the steps outlined above.

F. Ascoli, Department of Experimental and Biochemical Sciences, University "Tor Vergata", Rome, Italy, presented a report on molecular recognition between heme and globin in mini-myoglobin. One of the critical steps in the *in vivo* synthesis of hemeproteins involves inserting the heme into the protein pocket. This process requires molecular recognition between the heme and the polypeptide chain, which acquires the folding typical of the holoprotein native conformation. Recent views based mainly on structural studies of short peptides, that not only does folding of an initially synthesized protein occur, but also affects the subsequent folding of the rest of the molecule. It is not yet clear to which extent folding of the nascent chain and that of the molecule portion already synthesized are mutually affected, to reach the final native conformation of the protein, which may include disulfide bonds and other covalent modifications. This is of particular significance in the case of eukaryotic proteins, where the native conformation should be achieved through adjustments of the interactions of the different exon-encoded molecule domains.

Both the investigation of the folding pathway (sequential and/or posttranslational) and of the interaction between different portions of a protein encoded by a multi-exon gene, can be approached by studying the structural and functional properties of protein fragments obtained by limited proteolysis. Such an investigation is particularly suitable for hemoglobin, where molecular recognition between the heme group and the polypeptide fragment that provides the scaffold for the prosthetic group, requires the acquisition of a three-dimensional structure (*myoglobin folding*), with a typical functional property (controlled ligand binding). Ascoli presented data (limited proteolysis of horse myoglobin, circular dichroism and fluorescence spectroscopy, ligand binding, and dissociation kinetics) provide evidence that the protein fragment 32-139 of horse myoglobin, which corresponds closely to that encoded by the central exon of the myoglobin gene (residues 32-105), is able to recognize correctly the heme moiety giving rise to a *mini-myoglobin* This molecule requires a conformation resembling that of the corresponding segment in the intact protein with similar functional properties. However, circular dichroism (CD) experiments have shown differences in the alpha-helical content suggesting that, while the core of the molecule is packed as in the native protein, ensuring the correct functional behavior, the terminal segments (interrupted B and H helices) are somewhat unstructured and flexible. This is probably because of the loss of stabilizing interactions of neighboring residues.

I. Simon, Institute of Enzymology, Biological Research Center, Budapest, Hungary, presented a report on the regularities in amino acid sequences and their effect on the structure of globular proteins. Possibly, the structure of proteins possesses a special feature--it is the only structure in which all of the short overlapping segments of the polypeptide chain are in one of their significantly stable conformations. However, only polypeptides with special sequences can form such a structure. Simon and coworkers have demonstrated that short range regularities exist in the primary protein structure and they applied this knowledge to predict domain boundaries in multidomain proteins from their amino acid sequences.

Simon and coworkers have studied the range and measure of the regularities in question. The distances in the primary structure, where the appearance of the 20 x 20 amino acid pairs are significantly nonrandom, have been determined for each of these pairs. These distances (up to 8 residues) determine short overlapping segments sizes mentioned above, and the measure of the regularities were found to be directly correlated with the proteins' domain structure. The information obtained can also be applied in protein design to predict which amino acid replacements are acceptable for a protein.

J.P. Belaich, University of Provence, Marseille, France, discussed the cloning and sequencing of endoglucanases of *Clostridium cellulolyticum*. Belaich and colleagues recently isolated this bacterium--anerobic, mesophilic, and cellulolytic. Two cellulase genes isolated

from this bacterium were cloned in *E. coli* using plasmid pACYC184. Plamids pB52 and pB43 were purified from the transformants producing carboxymethylcellulase (CMCase) and the two cloned CMCase-coding genes were included in two EcoR1 fragments of 5.7 kilobases (kb) and 2.6 kb, respectively. The 5.5 kb EcoR1 insert of pB52 plasmid was restricted to a 2kb HpaII fragment that was subcloned in the pUC8 plasmid. The recombinant plasmid--pA24--conferred the CMCase phenotype to the host cell. The nucleotide sequence of the 2-kb insert of pA24 was established.

Thus, an open reading frame (ORF) of 1425 base pairs (bp) was determined. This ORF encodes a protein (EGCCA) of 475 amino acid (a.a.) residues with a predicted molecular weight of 53,630. Belaich and coworkers compared the nucleotide sequence and the predicted a.a. sequence of this endoglucanase with the published sequences of other endoglucanases and exoglucanases. A strong homology was found between the reiterated homologous segments of 24 a.a. located at the carboxyl end of the protein and the same conserved region previously found in three endoglucanases of the thermophilic bacterium, *Clostridium thermocellum*. The function of this region is under investigation. The plasmid pA24 was modified to put the gene under the control of the lac promotor. Belaich said that the new plasmid--A24.1--permits the production of enough endoglucanase for biochemical analysis; e.g., thermodynamic stability and specific amino acid alterations in protein.

H. Ludwig, Physical-Chemical Institute, University of Heidelberg, West Germany, spoke about studies on fluorescence measurements on the RNA-organizing protein (rop) of *E. coli* and some mutants as well as on the orientation of arginine for quenching tyrosine fluorescence and the position of the non-crystallizing part in solution. The studies were in collaboration with scientists at the European Molecular Biology Laboratory (EMBL) in Heidelberg.

The rop protein of *E. coli* is involved in the fine regulation of transcription of the Col E1 plasmid. According to Ludwig, rop is ideally suited for fluorescence studies for several reasons: (1) it has a single fluorophore, tyrosine 49 (Tyr 49); (2) several arginines (Arg) surround the tyrosine; this pattern is often part of a binding site; e.g., tendamistat, adenylate kinase, carboxypeptidase A, DNA polymerase I; (3) the X-ray structure of a major part is solved; and (4) the molecule can be modified by protein engineering.

Ludwig and colleagues investigated fluorescence decay of tyrosine (in peptides and the rop protein) using a picosecond fluorescence spectrometer based on a distributed feedback dye laser system with a streak camera. Reliable decay curves were obtained within two minutes and with only 3 ug of material. Time resolved fluorescence of a number of rop mutants was studied to obtain insight into the intramolecular quenching by arginine and the localizing of the noncrystallizing C-terminal part (tail, 7 amino acids).

In the wild type, tyrosine is surrounded by three arginines--Arg 13, 16, and 50. Replacement of Arg 13 or Arg 16 by Cys increased the fluorescence lifetime. On the other hand, the experiments showed that Arg neighboring Tyr in sequence had no quenching effect, probably because it is not well oriented. This observation was supported by lifetime measurements on extended peptides containing Arg and Tyr and on denatured rop.

From fluorescence lifetime – quantum yield and KI quenching experiments under low and high salt conditions on rop and on a mutant from which the tail was removed – Ludwig and coworkers deduced the position of the tail in solution. Under low salt conditions, the negatively charged tail bends back to the tyrosine region, which contains three positive charges. Increasing salt concentration screens the electrostatic interactions and the tail is removed from the Arg/Tyr region. This model is supported by the crystal structure of a further mutant where the position of the tail is known. The behavior of rop as described could be of functional importance; i.e., the tail might be a motility element regulated by the local salt concentration.

Behavior of Proteins in Alternate Solvent Conditions

P.L. Luisi, Polymer Department, Institute for Biotechnology (ETH), Hönggerberg (Zurich), Switzerland, presented information on the proteins solubilized in organic solvents via reverse micelles. Luisi said that certain surfactants dissolved in apolar solvents form spherical aggregates that are able to solubilize water in the form of a central water droplet (water pool) in their polar core. He and his coworkers have, in particular, studied the system, isooctane/AOT water, where AOT stands for bis (2-ethylhexyl) sodium sulfosuccinate. Their size, in the range of 20 to 100 Å, as well as several physical properties, depend primarily on the molar ratio of water to surfactant, $W_0 = (H_2O)/(AOT)$. At low W_0, the term reverse micelles is used. At larger W_0 values, the term water-in-oil-microemulsion is more correct.

Proteins, including a variety of enzymes (about 50), can be solubilized in the water pool without loss of activity and these can in principle be exploited biotechnologically; i.e., for the catalytic transformation of water-insoluble substrates.

The nature of the water in the water pool seems to be of central importance for affecting the activity and the structure of solubilized polymers. For example, the maximal catalytic activity is found at very low W_0 values, also for hydrolytic enzymes, and the stability is larger at smal-

ler water content. Also, at low W_0 values, water does not freeze at temperatures as low as -30°C.

Another biotechnological application of these systems has been seen in protein extraction and purification. Simply by shaking the protein powder with the AOT/isooctane microemulsion, proteins can be extracted into reverse micellar solutions. The specificity of the extraction process is affected by the micellar parameters (W_0, type of surfactant, concentration of micelles) as well as pH, presence of salt, pI of the protein. Here again, the maximal extraction power (also in the case of several small water soluble proteins) is found at low W_0 values.

The solubilization process efficiency is often very high (often the transfer into the microemulsion system is quantitative), and this poses the question of the thermodynamic forces responsible for the protein micellization. A thermodynamic study has shown that both electrostatic and entropic factors may be responsible for the solubilization process.

Large organelles; e.g., bacterial cells, spores, mitochomdria, and plasmids can be solubilized in organic solvents with the help of reverse micelles. The thermodynamic forces that are behind the solubilization and stabilization of these very large particles are not yet understood. Also the structures that are thus formed have not as yet been experimentally clarified. A concerted effort based on light scattering, nuclear magnetic resonance (NMR) spectroscopy, and electron microscopy is in progress by Luisi and his group to tackle the question of structure.

Microcalorimetry has also been applied to these systems in order to address some thermodynamic aspects of the structural problems. In particular, it has been used to determine the stoichiometry of water bound to AOT (the data being supported by ESR) and deuterium NMR experiments carried out in the Department of Biochemistry at ETH. Luisi and coworkers are also involved in the study of the thermodynamic stability of protein-containing reverse micelles.

Thermodynamics of Assembly, Stability, and Function of Biological Membranes

H.J. Hinz, Institute for Biophysics and Biophysical Biochemistry, University of Regensburg, West Germany, presented a report on the influence of head-group interactions on the miscibility of synthetic, stereochemically pure glycolipids, and phospholipids. Phase diagrams of binary mixtures of the glycerolipids 1,2-O-ditetradecyl-3-O-alpha-D-galactosyl-sn-glycerol (14-Gal) and 1,2-O-ditetradecyl-3-O-alpha-D-glucosyl-sn-glycerol (14-Glc) with the phospholipids L-dimyristoylphosphatidylcholine (DMPC) and L-dimyristoylphosphatidylethanolamine (DMPE) were recorded by high sensitivity differential scanning calorimetry (DSC) and used to determine the glycolipid-phospholipid miscibility in solid and liquid crystalline state. As a consequence of a metastable behavior of both glycolipids and DMPE, the solid state glycolipid/phospholipid miscibility was found to be strongly dependent on the temperature prehistory of the samples. While DMPC and 14-Glc mix continuously, the other three binaries displayed extended regions of solid-solid phase separation in the equilibrium low-temperature states. According to Hinz, the DMPE/glycolipid phase diagrams were of clearly expressed eutectic type. Continuous solutions were formed in the liquid-crystalline and in the metastable solid phases of the mixtures.

Simulations of the shape of the phase diagrams using the Bragg-Williams approximation showed certain deviations from ideal mixing in the liquid-crystalline continuous solutions. Since both glycolipids and phospholipids contain fully saturated fatty acids of equal chain length, their mixing properties were predominantly determined by the interactions between the lipid polar moieties, assuming the influence of ester- or ether-linkages of the alkyl chains on the mixing parameters to be negligible. According to Hinz, the clearly expressed differences in the mixing of 14-Glc and 14-Gal with phospholipids are most probably because of different hydrogen bond networks formed by the glucosyl and galactosyl residues.

Protein Function in Membrane Environments

W. Stühmer, Max Planck Institute for Biophysical Chemistry, Gottingen, West Germany, spoke about the oocyte expression system as a tool to characterize rat brain sodium channels. Stühmer said that the injection of *Xenopus laevis* (frog) oocytes with complementary DNA (cDNA) derived messenger RNA (mRNA) coding for various proteins is a valuable tool for the study of structure/function relationships. Stühmer and coworkers have used this type of system to characterize type II rat brain sodium channel or site-specific mutants thereof. Using patch pipettes, the steady state and kinetic properties of both macroscopic and single channel currents were measured. Wild type sodium currents showed properties similar to those reported for nerve and skeletal muscle. Two types of manipulations were performed.

- The sodium channel consists of four homologous repeats, each containing six transmembrane segments. There was little effect on sodium currents when the cDNA was cut between repeats I and III and both mRNA fragments injected. However, when the cut was between repeats III and IV, the inactivation time constant was slowed down drastically.
- Every third amino acid in the putative transmembrane segment S4 carries a positive

charge. Hinz and coworkers individually replaced these positively charged residues with neutral or negatively charged residues. In some cases, this resulted in little or no expression; in other cases, the potential dependence of activation was shifted to more positive potentials. This effect was cumulative, with shifts of up to 30 mv being found when two residues were changed simultaneously.

R. Glaser, Biophysics Department, Biology Section, Humboldt University, Berlin, East Germany (GDR), spoke about red cell shape dependence on membrane electric field as an example demonstrating the role of membrane electrostatics as a possible cellular control system. The living cell as a nonequilibrium system, produces an electrochemical gradient across the membrane using metabolic energy. This gradient generates an electrical field in the membrane depending on its ionic permeabilities. The membrane itself contains polar and charged groups, and probably mobile charges. The interaction of the phase boundary potential (transmembrane potential) with these charged elements of the membrane, influences the molecular membrane structure and consequently its functional properties. This gives a control system regulating various cellular functions.

In the case of human erythrocytes, the membrane electrostatics can be calculated in a reasonable way using thermodynamic approaches as well as the nonlinearized solution of the Poisson-Boltzmann equation. Glaser presented novel experiments on human erythrocytes with the aim of understanding this general mechanism, based on equilibrium as well as nonequilibrium processes. Glaser and coworkers demonstrated that Donnan potential as well as diffusional potential generated by ionophores (mystatine, valinomycin) and by modifications of ionic conditions (ionic composition, pH) strongly control the cell shape.

By modifying the transmembrane potential, cells can be transformed reversibly from cup-shaped cells (in the case of inside positive potential) into crenated forms (after depolarization to inside negative potential). This is the result of the delocalization of mobile membrane charges or of reorientation of dipols. The ion transport of erythrocytes was also found to be influenced by the membrane electric field, but not simply according to the electrochemical driving force. The ion transport is more or less protected against such field changes by electrosilent carrier systems.

H. Ruf, Max Planck Institute for Biophysics, Frankfurt, West Germany, reported on the subject of selective binding of alkali ions to a membrane-bound enzyme (Na,K-ATPase). Ruf and coworkers investigated the binding of alkali ions as well as of Mg^{2+} to a fluorescent derivative of membrane-bound Na,K-ATPase in buffered aqueous solutions at 37°C, employing a specially designed spectro fluorometric titration system that they developed. Ruf said that the modification of the native enzyme (isolated from the red outer medulla of pig kidney), by coupling of flourescein isothiocyanate (FITC) to a single lysine residue of the enzyme allows the detection, for example, of potassium binding by spectro fluorimetry, although the dye molecule is covalently bound to the region of the ATP binding site. All observed fluorescence intensity changes upon binding of cations can qualitatively be interpreted in terms of an equilibrium shift between two main conformations of Na, K-ATPase, one typical of the Na (E1) and one typical of the K (E2) complex.

The data of the titrations are analyzed in terms of 1:1 as well as of 2:1 complex formation. The model, which optimally describes K^+ binding, involves two binding sites per monomeric enzyme unit. The values of the corresponding macroscopic association constants K_I and K_{II} obtained from this analysis indicate a cooperative binding of K^+ ions. In addition, the studies performed in solutions of different composition revealed that buffers and salts like chorline chloride have strong effects on the characteristics of cation binding. These effects are not because of differences in ionic strengths and are interpreted as equilibrium shifts between the two main conformations (E1/E2).

Microscopic Thermodynamics of Coupled Celluar Processes

M. Coletta, National Research Center, Center for Molecular Biology and Department of Biochemical Sciences, University of Rome "La Sapienza", Italy, reported on a thermodynamic model for internal equilibria in zymogen activation. The mechanism of (pro)enzyme activation is a key event since its control has relevant effects on the regulation of metabolic reactions. This process has been extensively investigated in the case of serine proteinases, leading to the experimental evidence that it is a multistep mechanism.

Coletta proposed a thermodynamic model that represents an attempt to rationalize in general terms the actual knowledge about the activation process occurring in serine (pro)enzymes, using the trypsinogen-to-trysin transition as a functional model, also in view of the detailed structural information available. This model requires a network of interactions between structural domains that form the tertiary structure of the (pro)enzyme. Thus, the cleavage of the N-terminal polypeptide chain, which triggers the trypsinogen-to-trypsin activation process (and the consequent insertion of the newly formed Ile-Val N-terminal dipeptide into its specific binding pocket), alters, (1) the conformation of the primary recognition subsite (where micromolecular inhibitors such as benzamidine) bind, bringing about an enhanced catalytic rate of the enzyme; and (2) induces a

structural rearrangement of a set of recognition subsites affecting the interaction with macromolecular inhibitors such as Kunitz- and Kazal-type.

Thermodynamics Applied to Nucleic Acids

W. Thumm, Institute for Biophics and Physical Biochemistry, University of Regensburg, West Germany, presented an informative report on energy-structure correlations of plasmid DNA in different topological forms. He and his coworkers used differential scanning microcalorimetry (DSC), UV absorption, and CD to study structure and stability of linear (lin), open circular (oc), supercoiled (cd) and relaxed circular duplex (rd) DNA and calf thymus (CT) DNA. Investigations were made in low salt buffer and in the presence of 7.2 M $NaClO_4$. The chaotropic action of perchlorate promotes a reduction of the overall stability of DNA, which permits a direct determination of the transition enthalpies of all four DNA configurations. The stabilities against thermal denaturation were found to increase in the series lin $<$ oc $<$ cd $<$ rd. These relative stabilities can be rationalized on the basis of the linkage between supercoiling and secondary structural changes in topologically constrained duplex DNA.

On the basis of these studies, Thumm suggested a model of the melting process that is consistent with the energetic and spectroscopic data.

E. Patrone, National Research Center, Center for the Physical Chemical Study of Synthetic and Natural Macromolecules, Genoa, Italy, reported on the identification of structural domains in nuclear chromatin by DSC. The polynucleosomal chain is sharply divided into two structural domains, yielding independent contributions to the denaturation profile of chromatin. For instance, at low ionic strength, the unfolding of the linker can be easily distinguished from the one of the core particle by optical melting measurements. In the same way, the calorimetric scan of nuclei at physiological ionic strength contains the major information on both the higher-order structure of chromatin and the organization of scaffolding domains. The heat absorption curve of the nucleus is remarkably simple and is made up of five Gaussian endotherms at 56°, 66°, 75°, 92° and 107°C. This feature reflects the orderly array of the nuclear material in distinct compartments.

Patrone presented some results of the calorimetric approach to the structure of chromatin *in situ*. The nucleus of the rat liver hepatocyte was dissected by a mild digestion procedure and the denaturation of well-characterized components compared with the overall thermal profile. Scaffolding structure, including the proteins associated with heterogeneous nuclear RNA, were found to melt at 56° and 66°C, while the linker underwent a conformational transition at 73°C. More importantly, however, the denaturation of the core particle was found to be partitioned off, giving rise to both the 90° and 107°C endotherms. These transitions can be related to the denaturation of this domain placed within an extended loop and the higher-order structure, respectively. The ratio of the transition enthalpies represents a measure of the degree of condensation of chromatin and affords a thermodynamic tool for the quantitative investigation of the conformational changes underlying the progress of the cell along the cycle.

Symposium - Dynamics of Protein Development and Function

by Claire E. Zomzely-Neurath.

Introduction

This small focused and timely conference on the subject of the dynamics of protein development and function was held at the International Science Forum building of the University of Heidelberg, West Germany. The conference was organized by R. Zwilling, University of Heidelberg and H. Neurath, University of Washington, Seattle, U.S. There were 60 participants at this limited attendance meeting representing 6 Western European countries, the U.K., and the U.S.

Partial support for this meeting was provided by ONREUR. According to the organizers, there are no plans to publish the proceedings of the conference.

A large amount of material was presented during this 4-day intensive and informative conference. Thus, it is only possible to summarize selected topics in this report with emphasis on the research carried out by European scientists.

Flexibility and Rigidity in Proteins and Protein Pigment Complexes.

R. Huber, Max Planck Institute for Biochemistry, Martinsried Munich, West Germany, who shared the 1988 Nobel award in chemistry with J. Deisenhofer for his innovative research, presented a very interesting and informative talk on this topic. Proteins may be rigid or flexible to various degrees as required for optimal function. Flexibility at the level of amino acid side chains occurs universally and is important for binding and catalysis. Flexibility of large parts of a protein that rearrange or move are particularly interesting.

Huber differentiates between certain categories of large-scale flexibility although the boundaries between them are diffuse: flexibility of peptide segments, domain motions and order-disorder transitions of spatially contiguous regions. The domains may be flexibly linked to allow rather unrestricted motion or the motion may be constrained to certain modes. The polypeptide segments linking the domains show characteristic structural features. He illustrated the various categories with the following examples: (1) small protein proteinase inhibitors that are rather rigid molecules and provide binding surfaces complementary to their cognate proteases but also show limited segmental flexibility and adaptation; (2) large plasma inhibitors that exhibit large conformational changes upon interaction with proteases probably for regulatory purposes; (3) pancreatic serine proteases that employ a disorder-order transition of their activation domain as a means of regulating enzymic activity; (4) immunoglobulins in which rather unrestricted and also hinged domain motions occur in different parts of the molecule probably to allow binding to antigens in different arrangements; (5) citrate synthase that adopts open and closed forms by a hinged domain motion to bind substrates and release products and to perform the catalytic condensation reaction; and, (6) riboflavin synthase, a bifunctional multienzyme complex in which two enzymes (α and β) catalyze two consecutive enzymic reactions. The β-subunits form a shell in which the α-subunits are enclosed. Therefore, diffusional motion of the catalytic intermediates is restricted. In addition, Huber said that segmental rearrangement occurs in the assembly of the β-subunit. In contrast, rigidity is the dominant impression provided by the recent structures of the harvesting complexes and the reaction center involved in the photosynthetic light reactions. These are large protein pigment complexes in which the proteins serve as matrices to hold the pigments in the appropriate conformation and relative arrangement. Since motion would contribute to deactivation of the photo-excited states of the pigments and diminish the efficiency of light energy and electron transfer a functional role for the reduced flexibility is easy to rationalize for these proteins.

Folding Code for Proteins

R. Jaenicke, Institute for Biophysics and Physical Biochemistry, University of Regensburg, West Germany, presented an interesting talk on whether a folding code for proteins exists. The term *protein folding* refers to both the description of the spatial arrangement of the amino acid residues in a functional protein and the mechanism and kinetics by which the unordered (nascent) polypeptide chain achieves its native conformation in going from the one-dimensional to the corresponding three-dimensional structure. Faced with the astronomically high number of possible conformers of a polypeptide chain of average length, a surprisingly small number of *folding topologies* has been observed. Obviously, a given tertiary structure may tolerate a great number of amino acid exchanges without significantly changing its topology; the code of *protein folding* (if it exists) is highly degenerate. On the other hand, the majority of possible sequences does not seem to code for a defined functional protein; only a limited number of amino acid sequences yields a well-defined stable structure.

In vitro folding experiments have shown that small single-domain proteins may undergo fully reversible denaturation reactions. In multi-domain proteins, the acquisition of the native three-dimensional structure is determined by folding and merging of domains. To generate assembly structures, sequential folding and association must be coordinated such that specific recognition of "structured monomers" is achieved. The overall kinetic mechanism may be quantitatively described by a consecutive uni-bimolecular reaction scheme.

The question as to whether folding *in vivo* occurs as a co- or post-translational event, is still under dispute. What is certain is that domains represent independent folding units. Macro-assemblies are determined either by intrinsic form-determining properties of the protomers or by *assembly programs*.

Independent Folding of Protein Domains: Experimental Studies on Thermolysin

A. Fontana, Department of Organic Chemistry, CNR Biopolymer Research Center, University of Padua, Italy presented an informative talk on the above topic. In recent years, Fontana and his colleagues have studied fragments of the neutral protease, thermolysin, to address the question of the location, properties, and folding of protein domains. The central hypothesis of this work was that isolated protein fragments corresponding to domains in the intact protein are expected to fold into a native-like structure independently from the rest of the polypeptide chain, and thus resembling a small molecular weight globular protein in their properties.

Thermolysin shows a peculiar bilobal morphology with two distinct structural domains of equal size (residues 1-157 and 158-316) and the active site is located at the interface between them. Fontana and coworkers carried out detailed studies using protein fragments generated by cleaving the protein with cyanogen bromide at the level of the two methionine residues in positions 120 and 205 of the polypeptide chain of 316 amino acid residues. These researchers have shown that fragment 121-316, comprising entirely the "all-α" carboxyl-terminal domain is able to refold into a structure of native-like characteristics as judged by quantitative analysis of secondary structure from far ultraviolet circular dichroism (CD) spectra and immunochemical properties using rabbit antithermolysin antibodies. Also, fragment 206-316 was able to attain a native-like conformation in solution, as well as other shorter fragments generated by chemical fragmentation or limited proteolysis of fragment 206-316.

Overall, the results obtained demonstrate that it is possible to isolate stable and native-like supersecondary structures (subdomains or folding units) from globular proteins. Fontana found that the fragment 255-316 corresponds to the minimum size of a COOH-terminal fragment of thermolysin capable of independent folding. This 62-residue fragment (lacking disulfide bonds or bound metal ions) shows cooperative unfolding transitions mediated by heat (65°C Tm) and guanidine hydrochloride similar to those observed with small molecular weight globular proteins; e.g., ribonuclease. That fragment 296-316, prepared by solid-phase synthesis and comprising the COOH-terminal helix of thermolysin, is not folded in aqueous solution, but becomes helical when organic solvents or detergents are present.

These experimental data correlate well with the predicted location of domains and subdomains in the thermolysin molecule obtained using computer algorithms.

Protein Design

E. Sander, European Molecular Biology Laboratory (EMBL), Heidelberg, West Germany, spoke about the increasing importance of designed proteins. Recent work in protein design marks a new type of biological evolution. While until now, new protein molecules have evolved only as part of functional cells or organisms, they can now be modified and tested separately. The survival of newly designed proteins is no longer tied to the survival of a particular species, but is rather dependent on the dynamics of the evolution of human technology. Some examples of designed proteins are (1) point mutations in the nonpolar core of RNA-organizing protein (ROP); (2) active site graft onto ROP; (3) altered topology of ROP; and, (4) completely new amino sequences for classical folding units.

Molecular Structure and Function of S-Protein/Vitronectin and the Evolution of Other Members of the Pexin Gene Family

D.E. Jenne, Institute of Biochemistry, University of Lausanne, Switzerland, presented his and his group's work as well as that of other laboratories. Human complement S-protein, also called vitronectin, is implicated in various biological processes. The S-protein can mediate cell-to-substrate adhesion via an Arg-Gly-Asp sequence, which is recognized by the vitronectin cell surface receptor, and via a highly positively charged second site that binds to heparin and other glycosaminoglycans. During inactivation by antithrombin III, S-protein binds to modified antithrombin III, which is covalently linked to thrombin. Upon activation of the complement cascade, S-protein is incorporated into the nascent terminal complex in the fluid phase. The resulting SC5b-9 complex is cytologically inactive; whereas, the complement complex assembled on target cell membranes without incorporation of S-protein generates hydrophilic transmembrane pores.

The S-protein shares several structural and genetic features with hemopexin, transin, and interstitial collagenase. These four proteins are evolutionarily related and contain six to eight homologous peptide repeats. However, the first homologous peptide repeat of the S-protein, is preceded by two unrelated sequences – the somatomedin B domain and a highly negatively charged sequence. The latter acidic segment is sulfated at two tyrosine residues. A functional model for the S-protein has emerged from a comparison with other *pexins*.

The acidic tyrosine-sulfated segment probably interacts with the heparin-binding region in the native molecule that does not bind heparin. After a conformational transition, the acidic domain may interact with the heparin binding site(s) of antithrombin III exposed in antithrombin-thrombin complexes; whereas, the basic domain mediates binding to the negatively charged *C9-type* domains that are exposed in terminal complement complexes.

The Collagen Gene Family: Variations in the Molecular and Macromolecular Structure

K. Kühn, Max Planck Institute for Biochemistry, Martinsried (Munich), West Germany, said that 13 different collagen types presently are known. All collagen types have in common the triple helix that is combined with other structural elements such as globular domains and nonhelical parts. This leads to a large variety of macromolecular structures necessary to adapt the biochemical properties of the extracellular matrices to their numerous physiological functions. Kühn described the structure of

some typical collagen types and the principles of structural and functional variations of the collagen family.

The fiberforming type I collagen contains a continuous triple helix that gives the molecule the form of a stiff rod. In type IV collagen, which needs a more flexible molecule, as network forming collagen, the triple helical domain is frequently interrupted by nonhelical insertions that introduce into the molecule-related areas but to some extent also rigid kinks. The stability loss caused by these nonhelical imperfections is compensated by a higher content of hydroxyproline. Generally, the formation of the triple helix takes place after three alpha chains have been aligned in register with the help of globular domains located at their C-termini. Propagation of the triple helix occurs only from the C- to N-terminus. Three alpha chains connected in register via their N-termini do not fold into alpha helical structure.

In all collagens presently known, the globular domains are located at the ends of the triple helical domains. The fiberforming collagens use the globules as control elements, important for distinct post-translational events. Shortly before or during assembly of the molecules to fibrils, they are split off by specific enzymes. In other collagens; e.g., type I and VI, the globules are integral parts of the macromolecular structure acting as aggregation and cross-linking domains. In contrast to the multiglobular domain of type VII collagen, the anchoring fibrils fulfills a special function as contact and attachment site for other extracellular matrix components. The primary structures of the globular domains appear to be unique for collagen. So far, no homology to globular elements of other proteins has been found.

Alzheimer's Disease and the Amyloid Gene Product

K. Beyreuther, Center for Molecular Biology, University of Heidelberg, West Germany, presented his and his group's research as well as that from other laboratories. Alzheimer's disease (AD) is a human cerebral degenerative disorder characterized by gradual loss of memory, reasoning, orientation, and judgement. The memory impairment and intellectual function is correlated with amyloid depositions appearing mainly in the hippocampus and association cortex of the brain. The amyloid deposition is found in: (1) intracellularly as neurofibrillary tangles (NFT) in the cortex; (2) extracellular amyloid deposits in the cortex are found as neuritic plaques that consist of NFT-containing neurites surrounding an amyloid plaque core (APC); and, (3) a cerebrovascular amyloid (ACA) in the meningeal and intracortical blood vessel walls. The major protein component isolated from NFT, APC, and ACA is a small polypeptide of 4-4.5 kilodaltons (kDa), called A4 protein or β protein because of its relative molecular mass or a partial β pleated sheet structure, respectively. The brains of patients with Guamanian parkinsonism-dementia (Guamanian PD) have NFT and the brains of older individuals with Down's Syndrome (DS) (trisomy 21) have NFT, APC, and ACA that also contain the A4 protein as the major amyloid protein component. The identical sequences suggest that the amyloid in AD, DS, and Guamanian PD is derived from a common precursor protein and, furthermore, that a common mechanism may underly the formation of amyloid in these conditions.

Recently, AD's precursor has been characterized with respect to both nucleotide sequence and deduced amino acid sequence by isolation and analysis of a full length complementary DNA (cDNA) encoding a primary translation product of 695 residues--A4 precursor (PreA4). Northern blot hybridization reveals two transcripts of 3.4 and 3.2 kilobases (kb) in RNA preparations from fetal cortex indicating that more than one translation product is encoded by the PreA4 gene on human chromosome 21. The longer transcript is an alternative splicing form of the PreA4 gene containing an insert after the second domain and to encode a Kunitz-type protease inhibitor. The 695-residue PreA4 protein may be membrane spanning the N-glycan protein that displays the typical structural features of cell surface receptors; e.g., a N-terminal signal sequence followed by three extracellular domains, a transmembrane region, and a cytoplasmic domain of 47 residues.

The amyloid subunit--maximally either 42 or 43 residues long--corresponds to residues 597-639 of the precursor sequence. Therefore, about half of the amyloid A4 protein is derived from the putative transmembrane region residues 290-624 of the A3 precursor (PreA3) and contains the two potential N-glycosylation precursor sites. During amyloidogenesis, the C-terminal cleavage of the PreA4 has to occur within the transmembrane domain. Therefore, membrane damage is a possible primary event that must precede the release of small aggregating amyloid A4 subunit (suggested to occur at the clinical target sites).

The *curse* of protein folding resides in the PreA4 sequence corresponding to amyloid A4. The sequence includes two regions with a predicted tendency for β-sheet formation that will adopt an alpha-helical conformation when inserted into membranes. Without membranes, the β-sheet conformation required for amyloid formation is expected to dominate and to promote aggregation that finally results in amyloid.

Characterization of Proteins of the Mammalian Mitotic Spindle

H. Ponstingl, Molecular Biology Project on Mitosis, Institute of Cell and Tumor Biology, German Cancer Research Center, Heidelberg, West Germany, presented an

informative talk on the characterization of proteins of the mammalian mitotic spindle. This was a collaborative project with scientists from the University of Erlangen, West Germany and the Medical University Clinic, Graz, Austria.

Ponstingl and his colleagues used sera from patients with autoimmune diseases and monoclonal antibodies to localize proteins in the mitotic spindle by indirect immunofluorescence and to monitor their isolation from mitotic cell lysates. These antigens included 235 and 35 kDa polypeptides from the polar regions, a 200 kDa spindle protein with an interphase immunostain resembling dewdrops on a cobweb, and microtubule-associated proteins (MAP) of 180, 150, 130, and 110 kDa. Partial sequences were obtained from the 180 kDa MAP, indicating at least four variations of a common structural motif.

A kinetochore protein of 47 kDa was purified to homogeneity from HeLA cells. A hitherto unknown dynamic structure was detected by the serum of an endocarditis patient. The 33-kDa antigen is transported by the chromosomes to the metaphase plate where it is arranged in strings parallel to the long axis of the spindle. In anaphase, it remains at the equator and appears to be present at the cleavage furrow during cytokinesis. In addition, Ponstingl and colleagues have synthesized a new photoreactive derivative of vinblastine, that inhibits mitosis by binding to tubulin and upon intracellular activation by an argon laser overcomes chemoresistance of malignant cells.

Alcohol, Polyol, and Aldehyde Dehydrogenases

H. Jörnvall, Department of Chemistry I, Karolinska Institute, Stockholm, Sweden, spoke about his and his coworkers' research as well as that of other laboratories on alcohol, polyol, and aldehyde dehydrogenases. Alcohol dehydrogenases and related enzymes are represented by separate types of proteins. Zinc-containing proteins with about 40 kDa subunits constitute one line containing liver alcohol dehydrogenases. Nonmetalloenzymes with about 25 kDa subunits constitute another line including insect alcohol dehydrogenases. Both groups also contain other enzymes.

At least 20 different forms of the zinc-line proteins are now structurally known and several more are being analyzed. Only 22 residues are strictly conserved, covering a few functionally important residues at the active site and 11 Gly residues, which correspond to bends in the conformation of the horse liver enzyme, illustrating the importance of the backbone structure of the molecule.

Many forms in a single organism are explained by gene duplications at a minimum of three separate levels, illustrating successive steps of evolution. The most dissimilar forms (approximately 25 percent residue identities) have evolved into separate enzymes and exhibit considerable differences, also at the active site. The most similar forms (about 95 percent residue identities) represent fairly recent duplications, appear to be species-specific, and are true isozymes; i.e., the different forms of the typical liver alcohol dehydrogenase originally detected. In between, duplications have given rise to the alcohol dehydrogenases of different classes, constituting steps of differentiation between isozymes and separate enzymes, as originally distinguished for the human liver system but now known for several mammalian species.

Amino acid replacements allow structure/function correlations for all forms, and recently analyzed fish/avian alcohol dehydrogenases allow conclusions on the origins of the mammalian enzyme classes. Comparisons with aldehyde dehydrogenases and other dehydrogenases reveal still further properties and patterns.

Structure and Evolution of Alpha-Macroglobulins

L. Sottrup-Jensen, Department of Molecular Biology, University of Arhus, Denmark, discussed the structure and evolution of alpha-macrogloulins and the role of beta-Cys-G-Glu thiol esters in the proteinase binding mechanism. The complement proteins C3, C4, and C5, and the proteinase binding alpha-macroglobulins have a common evolutionary origin. The complement proteins C3, C4, and most alpha-macroglobulins contain internal beta-Cys-r-Glu thiol esters--a novel post-translational modification. These proteins are sophisticated examples of proteins regulated by specific limited proteolysis. When activated, they undergo characteristic conformational changes where biological activities are expressed not only in the final state but also in a short-lived nascent state. In the latter state, the activated thiol ester functions as a pseudoenzymatic site turning over once and for all, resulting in the covalent binding of these proteins to biological targets. Thereby, the targets become destined for clearance and destruction.

The group of alpha-macroglobulins comprise tetrameric, dimeric, and monomeric proteins as exemplified by human alpha2-macroglobulin (α2M), human pregnancy zone protein (PZP), and rat α1-inhibitor-3 (α1I3), respectively. Apart from the universal occurrence in the plasma and tissues of vertebrates, alpha-macroglobulins are also found in bird and reptile eggs--ovomacroglobulins--and in the hemolymph of some invertebrates.

The complete sequences of human α2M, rat α21M, α2M, and α1I3, and large segments of human PZP are now known. The overall degree of sequence similarity is 60 to 70 percent suggesting high structure conservation. However, the sequences of the activation cleavage regions--the *bait regions*--located near the middle of the ap-

proximate 1450 residue subunits are not only different lengths but show essentially no similarity, indicating a different evolutionary constraint for that region. The site(s) of activation cleavage for the five alpha-macroglobulins reflect the primary substrate proteinase requirement.

While the proteinase binding of the alpha-macroglobulin has been regarded as a *trapping* mechanism where only a relatively minor and variable fraction of different proteinases becomes covalently bound to the thiol esterified G1x-residues, the fraction of covalently bound proteinase is typically greater than 90 percent for many proteinases, particularly at low proteinase:alpha-macroglobulin ratios. It appears that although the tetrameric alpha-macroglobulins may utilize *trapping* as well, the dimeric and monomeric macroglobulins are solely dependent on the covalent binding potential in proteinase complex formation.

Peptides containing ε-lysyl (proteinase-r-glutamyl (α-macroglobulin)) cross-links in α113-chymotrypsin, and in α2M-trypsin, chymotrypsin, elastase, subtilisin, and thermolysin complexes have now been characterized. The major sites of cross-linking involve lysyl-residues located almost diametrically in two sectors along the surface, each sector having nearly the same orientation when viewed from the active site and substrate binding area of the proteinase being complexed.

In light of these results and current models of the structure of α_2-macroglobulin, Sottrup-Jensen discussed the interplay between bait region cleavage, conformational change, thiol ester activation, covalent binding, and exposure of receptor recognition sites.

Immobilization of Enzymes as an Approach to Unmasking

This topic was addressed by M.A. Coletti-Previero, INSERM Unit 58, University of Montpellier, France. The catalytic function of enzymes has been studied in environments where the water concentration was highly reduced. If enzymes are linked to appropriate supports, they can remain active within nonaqueous solvents and their catalytic action becomes solvent-dependent, meaning that sometimes unexpected reactions are promoted in addition to, or instead of, their natural activities.

Coletti-Previero presented examples concerning proteolytic enzymes covalently linked to alumina-phosphate complex, according to a new procedure recently optimized by her and her group. This new technique is a very flexible one and can be adapted to different requirements. More particularly, because of its unique characteristics, alumina allows the immobilization of enzymes combined with the minimum amount of water essential for maintaining their catalytic function in nonaqueous bulk medium. Under these conditions, activities, which are undetectable or extremely poor when enzymes are tested in a traditional way, can be rapidly unmasked under uncommon conditions.

A New Family of Proteolytic Enzymes

R. Zwilling, Zoological Institute, University of Heidelberg, West Germany, reported on studies by him and his coworkers concerning *Astacus* protease, representing a new family of proteolytic enzymes. *Astacus* protease is one of the major digestive enzymes in the stomach-like cardia of the crayfish *Astacus fluviatilis*. It occurs in homologous forms in all other decapode crustacea examined and has no known counterpart in other invertebrates or vertebrates.

The covalent structure comprises 200 amino acid residues in a single polypeptide chain, corresponding to a molecular mass of 22,614 daltons. The sequence appears to be unique since no homologous relationship to other protein families could be detected. A zinc atom in the enzyme's catalytic center seems to be ligated similarly to that in other zinc proteases. The enzyme liberates peptides with short aliphatic amino acids in the N-terminal position from protein substrates.

While no available inhibitor blocks the enzyme, Zwilling and his group have indications of inhibitory principles in plant extracts that might lead to the detection of new classes of inhibitors. They are pursuing studies of Astacus protease with respect to its mechanism, evolution, spatial configuration, and gene structure.

Human Leukocyte Elastase

W. Bode, Max Planck Institute for Biochemistry, Martinsried Munich, West Germany, reported on the specific interaction of human leukocyte elastase with various protein inhibitors. Human leukocyte elastase (HLE) is a lysosomal proteinase capable of degrading many connective tissue components. Normally, HLE is involved in the turnover of dead tissues and destruction of invading bacteria. Excessive release of HLE from leukocytes and/or reduction of its major natural plasma inhibitor, α_1-PI is often connected with severe tissue damage, as observed in pulmonary emphysema. The importance as a pathogenic agent has aroused interest in searching for appropriate protein inhibitors and designing potent synthetic inhibitors.

Bode and coworkers have solved and refined the high-resolution X-ray crystal structures of two HLE-complexes formed with a turkey ovomucoid inhibitor third domain and with a peptidylchlormethylketone as well as of the three potent protein inhibitors--human α_1-proteinase inhibitor (in its cleaved form), eglin C (in its complex with subtilisin), and SLPI/HUSI/MPI (in its complex with bovine α-chymotrypsin).

These protein inhibitors possess binding loops of virtually identical conformation around the reactive site bond; whereas, the remainders of their polypeptide chains are completely differently folded. Modeling experiments with crystallographically observed and/or computer generated HLE complexes can be compared with affinity data obtained from titration experiments and can be used to predict stronger or more selectively binding inhibitors directed against HLE.

Glucocorticoid Receptor Complexes

U. Gehring, Institute for Biological Chemistry, University of Heidelberg, West Germany, presented an informative report on his and his colleagues' studies dealing with dissociation and activation of heteromeric glucocorticoid receptor complexes. Steroid hormone receptors can be extracted from target cells as large heteromeric complexes of about 300,000 molecular weight provided that very mild extraction conditions are used that avoid denaturation and dissociation. These large structures are unable to interact with DNA. They contain the respective steroid-binding polypeptides in association with other macromolecular components, in particular, the heat shock protein--hsp 90. The large complexes of glucocorticoid receptors had been previously shown to contain only one such steroid-bearing polypeptide per complex. This polypeptide's molecular weight is 94,000 as shown by photoaffinity labeling and sodium dodecyl sulfate (SDS) gel electrophoresis.

Incubation at 20°C or exposure to high ionic strength leads to the dissociation of the large glucocorticoid receptor form and concomitant expression of DNA binding ability. Both dissociation and activation to DNA binding can be prevented by previously incubating the large complex with bifunctional reagents that crosslink the receptor components. The ability for dissociation and activation can be restored if a cross-linker is used that contains a cleavable group. Mild oxidation of the large complex with Cu^{2+}/O-phenanthroline prevents dissociation and activation presumably by forming disulfide bridges between subunits. Subsequent incubation with mercaptoethanol will restore the original ability for activation to DNA binding. The data suggest that diassociation of the large heteromeric receptor form is necessary and sufficient for activation. Furthermore, reversible cross-linking can also be achieved in intact cells.

Metallothionein

J.H.R. Kagi, Institute of Biochemistry, University of Zurich, Switzerland, presented an interesting report on spectroscopic features of metal-thiolate clusters in metallothionein. Metallothioneins (MTs) are widely occurring cysteine-rich polypeptides with a high affinity for group 2B and certain transition metal ions. Most mammalian forms contain 61 amino acid residues, among them 20 Cys whose positions are conserved in evolution. Their arrangement in multiple Cys-Cys and Cys-X-Cys sequences allows for binding of seven bivalent metal ions in two metal-thiolate clusters; i.e., $Me(II)_3$ $(Cys)_9$ and $Me(II)_4$ $(Cys)_{11}$ associated with the N- and C-terminal halves of the peptide chain, respectively. The resulting spatial structure, elucidated independently by X-ray crystallography and two-dimensional nuclear magnetic resonance (NMR) spectroscopy, is dumbbell-shaped with two almost equally sized globular domains around the metal clusters.

The formation of the metal-thiolate clusters in MT is a stepwise process governed by the metal supply. Thus, in titrations of apoMT with increments of Zn(II), Cd(II), or Fe(II) metal binding occurs at first at random in separate noninteracting tetrathiolate complexes. The clusters emerge only when the number of the unoccupied ligands becomes exhausted. This transition from mononuclear to oligonuclear complexes is associated with pronounced spectroscopic changes. Thus, cluster formation manifests itself by spectral shifts in the absorption and MCD spectra, and by conspicuous changes in circular dichroism (CD) from monophasic to biphasic ellipticity profiles. The latter effect can be attributed quantitatively to excitonic coupling of dissymmetrically oriented nondegenerate transition dipole moments located at the bridging sulfur ligands of the clusters.

The Evolution of Hemocyanins

B. Linzen, Zoological Institute, University of Munich, West Germany, presented an interesting report on the evolution of hemocyanins. Hemocyanins (Hcs) are the copper-containing, respiratory proteins of most molluscs and many arthropods. Being freely dissolved in the hemolymph, they are highly aggregated molecules; i.e., arthropodan Hcs (A-Hcs) are hexamers or multiples thereof that can be completely dissociated into subunits of about 70 kDa, while molluscan Hcs (M-Hcs) are composed of either 10 or 20 *compound subunits*, each comprising 8 or 7 *functional units* of about 50 kDa. The quaternary structures of A-Hcs and M-Hcs are radically different. Therefore, in spite of common spectral properties and the common function in oxygen transport, it has been much debated whether M- and A-hcs have a common origin or arose by convergent evolution.

The first two A-Hc sequences from *Eurypelma californium* (a tarantula) Hc, were published in 1983, and a series of others, complete and partial, have appeared since. No homology to other copper proteins was detected at that time. The tertiary structure of *Panulirus interruptus* (a spiny lobster) Hc reveals three domains.

Domain 2 contains the two copper-binding sites--Cu-A and Cu-B.

The sequence of a M-Hc functional unit is 90 percent different from A-Hc. However, 10 percent comprising the Cu-B site, are clearly homologous. This sequence also occurs in tyrosinases. While Cu-A in the tyrosinases and M-Hcs was newly developed, it arose by gene duplication in the A-Hcs. Thus, Linzen proposed an evolutionary tree of Hcs and tyrosinases. A-Hcs and M-Hcs should be regarded as two classes of respiratory proteins. In insects, which are typically devoid of respiratory proteins, a larval serum protein (LSP II) occurs that is homologous with Hc.

Conclusion

The presentations at this small focused conference about dynamics of protein development and function covered a wide range of research as shown by these summaries. It is clear that the European scientists' research is high quality.

There were many excellent presentations by U.S. scientists. Because ESNIB articles must be short, ONREUR must report research by European scientists, U.S. scientists, research cannot be included.

BIOTECH '88 Conference

by Claire E. Zomzely-Neurath.

Introduction

The biotechnology conference entitled BIOTECH '88 organized by Blenheim Online Ltd., was held at the Wembley Conference Center, London, U.K. The participants came from six Western European countries and the U.K. which had the largest representation. In addition, there were several attendees from the U.S. and Japan.

The forum of the conference included surveys of industry examining commercial strategies for success, the role of government, regulatory and managerial issues. In addition, there were reports on several areas of technology where development has been particularly impressive. The areas include: the commercialization of a new generation of thrombolytics such as tissue plasminogen activator (tPA); new techniques in bioprocessing; biodiversity and its importance for biotransformations; novel analytical systems including immunodiagnostics, DNA probes, biosensors, DNA sequencing and sensing and control in industrial processes.

The Proceedings of the conference are available from Blenheim Online Ltd, Pinner Green House, Ash Hill Drive, Pinner, Middlesex HA52AE, U.K.

Summaries of selected presentations are reported in this article.

New Developments in Downstream Processing Techniques

N.K.H. Slater, Bioprocessing Division, Unilever Research Laboratory, Vlaardingen, The Netherlands, presented a report on the topic of membranes for downstream processing of recombinant yeast products. Slater said that the development of materials and system modules has led to the replacement of many traditional processing techniques by membrane systems. This is particularly the case for processing recombinant organisms. According to Slater, benefits arise in improved process efficiency, simplicity, and robustness as well as in reduced capital and operating costs. He emphasized that the selection of appropriate membrane systems requires careful attention as membrane morphology, geometry, and surface characteristics influence transmembrane fluxes, selectivity, and resistance to fouling or loss of product caused by adsorption.

Slater reviewed the current commercial applications of membrane systems in the various sectors of biotechnology and examined the reasons why membranes may be preferred to other traditional approaches. He also discussed the factors that affect the selection of membrane materials. The latter was illustrated by work on the application of membrane systems for microfiltration and ultrafiltration in the downstream processing of broths containing recombinant yeasts (or yeast cell debris) for enzyme production.

J.M. Wyatt, EBS Ltd. based at the University of Kent, U.K., presented an interesting talk on pulsatile membrane separators for downstream processing. Wyatt said that crossflow membrane systems for microfiltration and ultrafiltration are increasingly being used in downstream processing to concentrate, recover, and purify microbial plant and animal cells, and biomolecules derived from them. According to Wyatt, such separators have low vol-

umetric efficiency because of low flux rates across the membrane and are prone to fouling.

Wyatt and colleagues have tested a novel crossflow membrane separator originally developed for aeration of blood (membrane lung) and plasmaphoresis for its wider potential in biotechnology. The separator consists of a sandwich of two membranes with the feed supply between them. Two outer compartments on either side of the feed channel act to collect the permeate. The membranes contain a large number of dimples concave to the inner channel. The feed supply is pulsed to give an oscillatory flow using a simple pumping system. According to Wyatt, this gives reversible rotating vortices, resulting in high efficiency of mass transfer. A five-fold increase in transmembrane flux is achieved with reductions in fouling, making these devices commercially attractive.

P.J.A.M. Kerkhof, Department of Chemical Engineering, Eindhoven University of Technology, The Netherlands, discussed some problems in membrane processing of enzymes. Kerkhof said that important aspects of enzyme ultrafiltration are yield, product quality, and processing capacity. He presented a case study in which attention was focused on the interrelation between processing conditions and the afore-mentioned aspects. The system considered was the batch ultrafiltration of a slightly thermolabile enzyme filtrate, containing also color components. According to Kerkhof, the product specification sets an upper limit to the product color, and thus diafiltration may be necessary. Some problems encountered are:

- Working at low temperature decreases thermal degradation rate, but also decreases ultrafiltration-flux, which may lead to unacceptable process times
- Working at higher temperatures leads to higher flux; however, because increasing degradation rate, a higher concentration ratio is necessary in order to meet the specified product activity. This may cause the overall process time to increase
- For a given membrane the enzyme retention increases with increasing transmembrane pressure; however, the retention of small color components also increases, thus requiring additional diafiltration.

Kerkhof said that simulations were carried out on the basis of models for these counteracting influences that led to an insight in possible areas in which the process is feasible. Also, the models can be used in economic optimization.

H.A. Chase, Department of Chemical Engineering, University of Cambridge, U.K., addressed the topic of the optimization of preparative liquid chromatography for the purification of biomolecules. Chase said that despite the wide variety of techniques used in the purification of biomolecules by liquid chromatography, a unified approach can be taken to the design and optimization of such processes. Optimization can be achieved by a combination of process design and process control during operation. The most important step in process design is the initial choice of the most suitable solid phase. The immobilized ligand dictates the specificity of the separation where as the matrix material affects the speed and resolution of the separation. An efficient preparative separation is not always achieved by the scaleup of analytical techniques, according to Chase. Highly selective separations are particularly appropriate for preparative use and do not necessarily involve the need for large-scale high-performance liquid chromatography (HPLC) equipment. A simple model of liquid chromatographic separations can be constructed but characteristic parameters have to be determined from small experiments. These models can be used as the basis for the design and optimization of large scale methods. Additional optimization can be achieved during operation by efficient process control. This requires the ability to be able to monitor the separation in an on-line manner. According to Chase, the use of rapid affinity chromatographic monitoring (RACMON) provides an effective means of acquiring the required information.

Immunodiagnostics

J. Chesham, Immunoassay Group, Cambridge Life Sciences Co., U.K., discussed future trends in diagnosis and monitoring. New developments in immunodiagnostics will be aimed at improving the speed of diagnosis and the convenience of use. The rapid flow-through devices, currently available are a step in the right direction. However, the ultimate aim must be to develop tests that involve only the application of sample, a minimum incubation time (about 1 minute) and visual interpretation of the result. Multilayer dry-film techn[illegible]ost likely to satisfy these criteria. Increased co..abo..ation between the materials scientist engineer and immunochemist will no doubt improve the chances of this goal being realized.

Chesham also anticipates that the combination of advanced sensing techniques coupled with immunoassay will result in the emergence of immunosensor devices. These techniques, which have recently received a high profile in the scientific literature, are now becoming a reality. The eventual aim will be to produce a hand-held instrument which, after the addition of a small volume of the test sample; e.g., milk, plasma or extracted toxin, will give a direct reading of the amount of analyte present. The technical difficulties may be enormous, but 15 years ago no one would have thought that visually interpretable immunoassays would be available in such a short time.

W.P. Collins, Diagnostics Research Unit, King's College School of Medicine and Dentistry, London, U.K., reported on the subject of alternative optical

immunoassays. There is now a trend towards the development of rapid, self-contained immunoassays with an optical endpoint. The antigen/antibody reaction time is being decreased by different methods of immunoconcentration, and monitored by the use of appropriate labels for endpoints based on photon absorption, scattering, or emission. The tests are being made self-contained by the spatial orientation and generation of solid and liquid phase reagents.

Optical immunoassays are being applied extensively to problems in clinical medicine, and to a lesser extent to analyses in veterinary, forensic and environmental sciences, agriculture, horticulture, and the food industry. The current world market for reagents, kits, and instruments has been estimated to be greater than $2 billion.

Currently, the concentration of analytes covers at least 12 orders of magnitude, from millimoles to femptomoles. Furthermore, the concentration of each individual analyte covers at least three to four orders of magnitude during the course of a lifetime. However, more sensitive methods are still required for the detection of tumor markers and bacterial and viral antigens.

New technological developments underway, according to Collins involve

- Development of integrated sampling devices for biological fluids
- Use of alternative labels for binomial and highly sensitive tests
- Use of standards for quality control and quantitation
- Development of small readers for immunotubes or immunostrips.

Immunoassay development is still required for

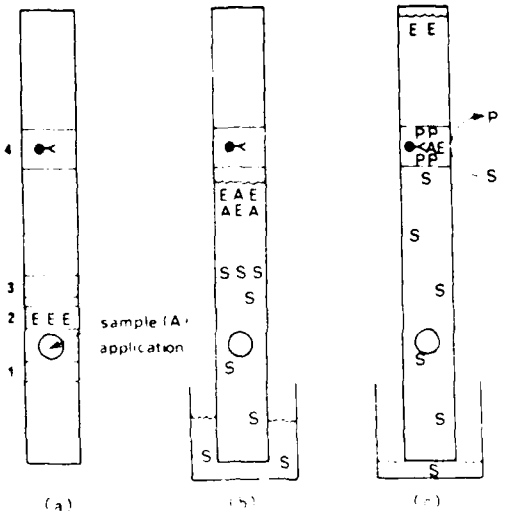
- Novel analytes measurement
- Increased assay sensitivity; e.g., for viral and bacterial antigens and tumor markers
- Increased working range of analyte (to reduce the need for sample dilution)
- Multiple analytes measurement in the same sample; e.g., hormone profiles
- Tests production with a long shelflife under unfavorable conditions
- National and international standardization.

With the advent of self-contained immunoassays, more emphasis will be placed on the source and preparation of appropriate samples for analysis.

J.F. Wright, Manufacturing Development, Boots-Celltech Diagnostics Ltd, U.K., reported on a simple immunodiagnostic test system--immunostrip--for the alternate site market. During the past few years, many advances in biochemical assay and related technologies, encouraged to some extent by market forces, have meant that the diagnostic test, once confined to specialized laboratories, can now be executed in a range of nonlaboratory situtations. These *alternate sites*, as they are often called, include the physicians' offices, emergency rooms, clinics, and, in some cases, even the home. The expansion of the testing arena is not restricted to the area of human diagnostics and many exciting developments are occurring with veterinary and agricultural applications such that *field testing* is becoming a reality. The resulting significant increase in the number of potential test users means that the alternate site market is, and will continue to be, of increasingly important to the future of the diagnostics industry.

The developing alternate site sector of the diagnostic test market requires certain characteristics of a suitable test system, including simplicity, ease of use, robustness, and stability. He described an *immunostrip* system that combines the principles of immunochromatography and enzyme immunoassay technology allowing the design and manufacture of very simple, sensitive, and quick immunoassays for alternate site nonlaboratory testing situations.

The *immunostrip* consists essentially of an enzyme-linked immunoassay carried out on a length of bibulous glass fiber paper. The labeling enzyme is horseradish peroxidase (HRP) which uses a colorless substrate including tetramethyl-benzidine (TMB). The strip of paper (15x1x0.1 cm) is arranged so that the developing solution (about 2 ml) can be applied to one end. The various reagent components necessary for the functioning of the immunoassay are deposited and dried onto the paper at specific locations along the strip (Figure 1).



Basic Principles of Operation of the Immunostrip: Reagent zones 1-4

E = enzyme (HRP) conjugate
A = sampale analyte
S = enzyme substrate component (TMB)
P = enzyme product
⊷ = immobilized antibody

(a) initial strip, (b) mid development, (c) development complete

Figure 1.

The sample solution is applied towards the beginning of the strip and the test is initiated by bringing the end of the strip into contact with the developing solution. This solution migrates along the paper by capillary attraction dissolving the various reagents (including one that is the enzyme conjugate reagent) and mixing with the sample in the zone at the solvent front.

The basic principles of the *immunostrip* can be applied to a wide variety of immunoassay formats by carefully selecting and positioning reagents on the strip. Hence, it is possible to produce tests for a complete range of analytes of interest in the areas of clinical chemistry, microbiology, food, agriculture, and veterinary applications. Perhaps the two formats with most applications, according to Wright, are the immunometric assay and the competitive (hapten assay).

Advances in DNA Probe Technology

M.A.W. Brady, Research Division, Amersham International Co., U.K., presented a report on progress towards nonradioactive labeling and detection of nucleic acids. Brady said that progress with satisfactory nonradioactive labeling and detection of nucleic acids has been slower than expected; this in part has led to delays with the development of the probe assay business. Recent work has led to the discovery of a number of innovative approaches, both in new detection technologies and in amplification procedures of either target or probe which reduces the dependence upon high sensitive detection. Brady reviewed these developments.

Recent advances in nucleic acid labeling and detection technology include target amplification and amplification of the hybridized probe. The detection of messenger RNA (mRNA), as opposed to DNA from which it originates, is the first example of target amplification. This approach was further extended by GenProbe (U.S.) who have based several assays on ribosomal RNA. Since many organisms have multiple copies of ribosomal RNA that are genus and type specific, this instead of DNA can be used as a target identification sequence. It is suggested that this approach provides an amplification factor of about 10. A range of kits using this principle (some FDA-approved) has been launched by GenProbe. The inital products are based on radioactive detection, but more recently, their first nonradioactive product using chemiluminescence was launched. A further major advance was made by Cetus (U.S.) with the development of their polymerase chain reaction. Unlike the ribosomal RNA, this applies principally to DNA. Once a target sequence is known, it can be copied in a virtual exponential manner by successive primer extension reactions; up to 200 may be required for high copy amplification. The convenience of this process has been markedly improved by (1) the availability of equipment to aid the many enzyme cycles involved and (2) a thermostable enzyme has been identified to survive the higher temperatures of strand dissociation. Amplification factors of $10^5/10^6$ are claimed. This process works successfully in research applications and HIV assays (AIDS) of infected cells. For amplification of the hybridized probe, initial assay approaches have been based on sandwich hybridization, but recently new approaches have been developed that amplify the hybridized probe as opposed to the target. A system developed by Chiron Corp. (U.S.) derives its amplification via a series of chemically cross-linked oligonucleoties, amplification multimers, that have been specially designed to hybridize both to a single-stranded probe that is target specific and to a single stranded probe to which the horseradish peroxidase label is attached. Detection is then either colorimetric or based on enhanced chemiluminescence. The stable hybridization complex results in an amplified number of reporter/detecton molecules with a consequent improvement in assay sensitivity and convenience.

Some other advances in nucleic acid labeling and detection technology, according to Brady are

- High sensitivity detection systems using acridium esters, horseradish peroxidase enhanced chemiluminescence, alkaline phosphatase enhanced chemiluniscence
- Ribonucleae enzyme amplification system
- Assays that rely on the interaction between two fluorescent groups attached to complementary strands of DNA
- The use of liposomes to enhance immunoassay sensitivity has been explored and an analagous system could be used for probe assays
- *In situ* hybridization – still too time-consuming but is being improved.

A.C. Syvänen, Orion Genetic Engineering Laboratory, Orion Corp. Ltd, Helsinki, Finland, presented a report on affinity--based hybrid collection--a rapid method for the detection of specific nucleic acid sequences. Nucleic acid hybridizations proceed faster in free solution than in mixed phase reactions and that the separation of free probe from hybrids is a major problem after solution hybridizations. Syvänen and her colleagues have devised a nucleic acid hybridization assay in which a pair of probes recognizing the target DNA are used. One of the probes is modified with a ligand to enable collection of the formed hybrids on an affinity matrix. The other probe carries a detectable label to allow quantification of the collected hybrids. Within radiolabels, a sensitivtiy of 5 x 10^5 genomes can be achieved. She also said that the assay method was coupled to the polymerase chain reaction for a major increase in sensitivity.

Biosensors

F.J. Rowell, Department of Pharmaceutical Chemistry, Sunderland Polytechnic, U.K., presented an interesting report on receptor-based biosensors. Rowell said that biological membrane-bound receptors possess attributes which commend them for consideration as sensing devices for use in biosensors. These include specificity for a variety of analytes such as drugs and hormones, and the physico-chemical changes that occur as a consequence of the binding interaction and that have the potential for use in signal generation and transduction. Rowell discussed the sources of receptors, from tissues and from cloned complementary DNAs (cDNA). He also presented data on the stability and ligand-binding kinetics of membrane-associated and solubilized receptor preparations for muscarinic, benzodiazepine, and serotonin receptors. In addition, Rowell discussed the current limitations of receptors and their future potential.

Rowell said that sheep brain receptors that have been studied have similar binding affinities and kinetic properties to those observed for the corresponding polyclonal sheep antisera binding the same H^3-ligands (haptens). However, the receptors generally exhibit lower specificity than the corresponding antibody/hapten combination. In contrast to antibodies, the membrane-bound and solubilized receptor preparations are much more difficult to purify and concentrate since they are much less stable than antibodies. According to Rowell, if methods can be developed to increase the yields of receptors through genetic engineering, they could find potential application in biosensors as substitutes for antibodies for the detection of certain analytes. Alternatively, further studies on their structure and function particularly with respect to ion-gated mechanisms could lead to the design and synthesis of analogues with more robust and attractive properties for use in biosensors.

C.F. Thurston, Bioelectrochemistry and Biosensors Group, King's College, London, U.K., spoke about advances in electrochemical enzyme biosensors, in particular the glucose sensor using glucose oxidase/platinized carbon paper (GOPCP) electrode. Thurston described the properties of an amperometric sensor employing glucose oxidase immobilized on platinized carbon paper as a model for assessment of the state of development of amperometric enzyme sensors. For the measurement of glucose, the system provides a large rapid response in the range of concentration required for clinical analysis, and the stability properties of the electrode are excellent. The electrode can be miniaturized and can be employed for glucose measurement at much lower concentrations. According to Thurston, the coimmobilization of additional enzymes with glucose oxidase to allow the measurement of other analytes is exemplified by a three-enzyme sensor for sucrose.

Sensing and Control in Industrial Processes

D.J. Clarke, Sensor Group, Division of Biotechnology, Center for Applied Microbiology & Research (CAMR), Porton Down, U.K., spoke about the use of sensing for fermentation. The monitoring and control of most fermentation processes rests with relatively few parameters--temperature, pH, dissolved oxygen, carbon dioxide, agitation rate, foaming, and, in a few cases, redox potential. Electrochemical dissolved oxygen probes and conductimetric foam probes are still insufficiently reliable for some industrial processes. However, there have been some improvements in the monitoring of some conventional parameters. Biomass monitoring is viewed as particularly important and development of probes capable of providing a range of information is important (especially, total particulate mass, cellular volume fraction, metabolic activity, culture contamination, enzyme production). These aspects were discussed by Clarke. In addition, Clarke spoke about the development of a multiprobe containing low cost, solid state sensor arrays for monitoring a range of biochemical parameters (in particular, ammonium, potassium, sodium, calcium, magnesium, glucose, lactate, acetate and glutamine).

R. Carr, Biotechnology Division, CAMR, Porton Down, U.K., discussed the applications of dynamic light scattering to biotechnology. Dynamic light scattering techniques such as Photon Correlation Spectroscopy and Laser Doppler Velocimetry have been applied to a number of biotechnological processes. For example, the analysis of microbial cultures for the rapid monitoring of microbial contamination, the on-line monitoring of protein purification by liquid chromatography, and the analysis of flow profiles within an air lift fermenter. The technique is capable of being configured as a fiber optic mediated system and using solid state laser light sources and detectors.

The subject of microbial physiology for bioprocess control was addressed by D.E. Brown, Biochemical Engineering Department, Cranfield Institute of Technology, U.K. The knowledge of the physiology of microbiological processes is creating a foundation on which it is possible to develop meaningful control strategies. Improved methods of measurement and the availability of microcomputers are resulting in a number of successful feed back and feed forward controlled processes. There is a need to improve the potential of bioprocess control by using synthetic medium components to replace the ill-defined and often variable natural products present in many industrial formulations. Brown thinks that this will lead to the successful application of many new measuring devices and reliable optimization procedures.

DNA Sequencing-Development and Applications

W.J. Martin, Biotechnology Center, University of Manchester, U.K., discussed the topic of instrumentation for automated DNA sequencing and developments in Europe, Japan, and the U.S. Several programs aimed at automating aspects of the DNA sequencing process are underway in Europe, Japan, and the U.S. The U.S. program has become part of the Human Genome Sequencing Project recently endorsed by the National Academy of Science. Thus, many commercial instrument companies are developing systems to accelerate DNA sequence data capture. A Japanese project to automate DNA sequencing has been underway for 6 years, coordinated by a national committee with representatives from universities, research institutions, and instrument companies. On the other hand, the European approach, in this area, has been rather fragmented and poorly funded with various programs in academic, commercial, and research institutions in several countries mostly operating separately with little inter-European coordination.

Martin mentioned some of the European instrumentation developments in DNA sequencing. The European Molecular Biology Laboratory in Heidelberg has been responsible for many innovations in sequencing techniques including a method for purifying DNA templates and a system for separating fluorescently tagged sequence mixtures and imaging the resulting band patterns in real time using laser excitation.

A scintillating fiber optic sensor to image radiolabeled Beta-emmiting DNA bands has been developed at the Institute of Nuclear Physics, University of Paris Sud, and image analysis of biosystems is underway at the University of Paris 7.

A group in the East German Academy of Science has carried out extensive investigations of (Maxam/Gilbert) sequencing on solid supports (CCS and DE81 anion exchange papers). The Swiss company, Genofit, has announced plans to market a Beta-scanner to directly image band data from radiolabeled sequencing gels.

Martin said that a number of systems to automate discrete aspects of the Sanger DNA sequencing process have been constructed at the University of Manchester Institute of Science and Technology (UMIST) and are under further development in the Manchester Biotechnology Center, UMIST, with European Economic Community (EEC) funding in collaboration with colleagues in the Rutherford Appleton Laboratory, U.K., the University of Constance, West Germany, and the Transfer Center Constance for Image Data Processing. They include: (1) an automatic reagent manipulating system, the ARMS device, constructed at UMIST, which measures, dispenses, and mixes microliter volumes of reagents for reaction at controlled temperatures; (2) automatic direct-blotting electrophoresis units that have been built at the University of Constance to separate DNA sequences and other macromolecular mixtures and transfer the bands directly to moving membrane (Hofer Scientific Instruments are marketing a version of this system); (3) a multi-wire proportional counter developed for the Manchester Biotechnology Center at Rutherford Appleton Laboratory will scan a complete sequencing gel and digitize the band pattern; and (4) a machine vision directed robot (APSCIR) under construction at the Manchester Biotechnology Center, UMIST, that selects bacterial colonies or plaques from petri dishes as part of a project funded by the EEC. The colonies or plaques will be automatically harvested and innoculated into discrete containers for further growth. A number of the above devices are being commercialized by an EEC instrument manufacturer.

P.G. Debenham, Scientific Services, Cellmark Diagnostics, U.K., spoke about genetic fingerprinting. In 1985, Dr. Alec Jeffreys published his discovery of DNA sequences which, when used as probes, could identify a unique pattern in everyone's DNA. The pattern, known as DNA fingerprint, or genetic fingerprint can be obtained from any nucleated cell in the body. ICI Diagnostics, through Cellmark Diagnostics, is now making this technology available to forensic forces around the world and the general public at large. Apart from forensic work, DNA fingerprinting is being used to ascertain paternity, prove family relationships, and to analyze animal pedigrees.

Conclusion

The biotechnology conference, BIOTECH '88, dealt with an overview of many aspects of biotechnology as well as recent developments in biotechnological areas such as bioprocessing, biotransformations, biosensors, immunodiagnostics, and DNA probes. Many of the presentations were by scientists from R&D divisions of industrial concerns and show that these scientists are carrying out top level research as well as those in academia. The summaries contained in this report were based on talks by European scientists. There were several excellent presentations by U.S. and Japanese scientists that could not be included in this report.

Advances in Purification of Recombinant Proteins: Interlaken, Switzerland--First Conference

by Claire E. Zomzely-Neurath.

Introduction

This timely and informative conference on advances in purification of recombinant proteins was held in Interlaken, Switzerland, March 14 to 17, 1989. Since the conference was planned as a small, focused meeting, the attendance was limited to 154 particpants. However, the widespread interest in this important area of research in biotechnology was manifested by the many countries represented among the participants. Twelve Western European countries (with France and Switzerland having the largest representation), in addition to the U.K., constituted the bulk of participants. However, other countries represented included the U.S., Canada, Israel, Japan, India, New Zealand, and Taiwan. In addition, there were participants from the U.S.S.R., Hungary, Czechoslovakia and East Germany (GDR) making this a truly international group of attendees. Because of the nature of the conference, 74 percent of the attendees were from R&D divisions of industrial concerns with the balance from academic institutions.

The conference was sponsored by the Swiss Coordination Committee for Biotechnology (S.C.C.B.) and the French organization, Gene and Research on Biotechnology of Proteins (G.R.B.P.).

In addition to the oral sessions, there were poster presentations as well as two roundtable sessions. The topics covered included a range of methods for purification of recombinant proteins. According to the organizing committee, there will not be a publication of the proceedings of this conference.

Summaries of most of the oral sessions are included in this report. A couple of very general presentations are omitted as well as a report on U.S. Federal Drug Administration (FDA) regulatory requirements for recombinant products which was given for the benefit of the European R&D scientists.

Strategies in Downstream Processing

M. Scawen, Division of Biotechnology, Center for Applied Microbiology and Research, Porton Down, U.K., presented an overview of this topic. Strategies in downstream processing technology no longer rely solely on the inherent properties of the native protein or enzyme to be purified. In addition to the development of new fast flow high resolution spherical matrices, aqueous two-phase systems, large-scale affinity and immuno-affinity purification regimes and membrane ultrafiltration and ion-exchange systems, other areas involving upstream factors have begun to influence protein purification methodology. Thus, recombinant DNA (rDNA) technology has led to the increasing observation of insoluble bodies under conditions of high expression formed of at least partially denatured protein that require specific solubilization and renaturation technology, particularly difficult on a large scale. Scawen also said that the capability of employing specific signal peptide sequences to promote secretion of proteins into either the periplasmic space or extracellular medium has also been explored. Other genetic techniques have also been used such as specifically altering the charge on a protein by C-terminal tailing with several arginine residues; fusing the protein to be purified to another readily purifiable protein, such as protein A; and the introduction of specific protease cleavage residues into hybrid fused proteins to allow subsequent separation of the two moieties.

Extraction as a Method in Protein Purification

B. Mattiasson, Department of Biotechnology, Chemical Center, University of Lund, Sweden, discussed this topic in which he and his group have considerable experience. Mattiasson said that extraction is a unit operation that is well known and routinely used in traditional applied chemistry. However, the separation of proteins is more complicated: rather few extraction media can be used without denaturing the protein molecules. The choice of extraction medium is very much a function of surface chemistry. Organic solvents are generally not suitable because in most cases the proteins are insoluble and may easily be denatured. Extraction by the use of microemulsions is still in its infancy, making its potential difficult to judge.

According to Mattiasson, the most well known extraction system for proteins and other biological macromolecules is two-phase aqueous systems based on polymer/polymer or polymer/salt solutions. Such systems contain 80 to 95 percent water in both phases with a very low surface tension between the phases. Furthermore, a very low energy output is required for mixing, which is advantageous. In general, polyethylene glycol (PEG)/dextran and PEG/salt are used for the two-phase system.

However, dextran is quite expensive and a new substitute for dextran is also being used by Mattiasson and his group. It is called Reppal PE 200 and is only one-fifth the cost of dextran.

Mattiasson said that spontaneous partitioning of proteins may be sufficient in some cases. Otherwise, affinity partitioning is used as a powerful and versatile complement.

Aqueous Two-Phase Partitioning for the Purification of an Enzyme Produced by Mammalian Cell Culture

J.P. Lenders, Pharma Development, Sandoz Ltd, Basel, Switzerland, presented an informative talk on this subject. Lenders said that in the purification of proteins produced by mammalian cell culture supplemented with fetal calf serum, small quantities of proteins have to be separated from large amounts of bovine serum albumin (BSA). Lenders and his coworkers tested two-phase partitioning (ATPP) for such a separation. This method has a high capacity for proteins and a good selectivity can be achieved by adjusting the experimental conditions.

Lenders and colleagues tested the classical PEG/dextran and PEG/phosphate systems. The BSA-partitioned preferentially in the dextran or the phosphate bottom phase, while the enzyme (urokinase) to be separated could be forced into the PEG top phase by increasing the ionic strength of the system.

In a typical experiment, the total protein content was 1.1 percent and the two-phase system was composed of PEG 4000 6 percent-K HPO 7 percent-NaCl 8 percent (all w/w), pH of 7.3. The partition coefficient (K) was 0.08 for BSA, and 3.4 for the enzyme. Hence, 98 percent of BSA was in the bottom phase and 2 percent in the top phase. The specific activity of the enzyme was enhanced by a factor of 28 in one step. The recovery yield of the enzyme was 51 percent for the first extraction as a result of an unfavorable bottom/top volume ratio of the two-phase system, equal to 3.5/1. Lenders said that this yield could be easily enhanced by multiple extraction.

Lenders considers that ATPP turned out to be a useful purification procedure for proteins from cell culture and could possibly be an alternative to ion-exchange chromatography.

Centrifugation/Filtration

W.C. McGregor, Technical Development, XOMA Corporation, Berkeley, California, U.S., discussed this very important aspect of protein purification. The primary separation steps after the bioreactor are often referred to as the isolation segment of downstream processing. Typically, during isolation, the objective is to separate the product from the cells, cell debris, and other particles by centrifugation and/or filtration and then reduce the volume (remove water) often by membrane filters.

According to McGregor, a decision must be made early in process development whether to proceed with conventional isolation routes as described above followed by a series of purification columns or to develop a series of liquid/liquid extraction steps. The choice may depend on the level of purity required at the end. For the production of highly purified therapeutic proteins, some processing of the product/process stream through a porous media (filter) is usually required for the removal of trace contaminants.

McGregor said that although centrifugation continues to be an important primary step, particularly for the isolation of inclusion bodies, most of the new isolation developments have been in the area of membrane filter separations. Examples include: (1) broader, new applications of cross-flow filtration, and (2) new membrane materials such as ceramics, porous glass, bacterial cell envelope layers and new polymer compositions. New rotary configurations have been developed to improve shear rate during crossflow.

According to McGregor, a major practical hurdle for the application of porous media in separation of biological products continues to be fouling of the separation surface.

Clarification of Cell Lysates

K. Fletcher, Bioprocessing Research, Rohm and Haas Co., Philadelphia, PA, U.S., spoke about the clarification of cell lysates; i.e., removal of cell debris, nucleic acids and endotoxins using submicron-sized polymeric particles. The work presented was a collaborative project with C.W. Kim and C. Rha, Biomaterial Science and Engineering Laboratory, Massachusetts Institute of Technology, Cambridge, MA, U.S.

Fletcher said that negative charges on cell surfaces, nucleic acids, and endotoxins were utilized for clarification of cell lysates. Positively charged submicron-sized polymer particles (SSPP) selectively absorbed cell debris, nucleic acids and endotoxins while retaining product proteins in solutions, thus facilitating easy removal of complexes by sedimentation or centrifugation. Therefore, according to Fletcher, cell debris, nucleic acids, and endotoxins can be removed concurrently in the initial stage of downstream processing. The SSPP used in these studies was BiocrylR bioprocessing aids (BPAs), a product of Rohm and Haas Company.

Clarification of *E. coli* and *S. cerevisiae* lysates was carried out and the absorbance of the supernatants decreased to less than 0.01 at 600 nm. Furthermore, the energy and power required for centrifugation in removal of cell debris was reduced to 5 and 10 percent, respective-

ly. Concentrations of nucleic acids were lowered four orders of magnitude with the addition of 4 mg SSPP/ml of cell lysate, a reduction of seven orders of magnitude. Therefore, according to Fletcher, SSPP can accomplish a very effective clarification of cell lysates.

Refolding of Denatured Recombinant Human Interferon Produced from S. cerevisiae

M.C. Casagli, Sclavo Research Center, Sienna, Italy, presented her's and her group's work on this topic. Human immune interferon, a soluble eukaryotic protein, was expressed in *S. cerevisiae* (yeast) as an insoluble product. Insolubility appeared to result from the formation of intracellular protein aggregates (inclusion bodies). Inclusion bodies can be released by mechanical disruption procedures and recovered by centrifugation.

Since denaturation is essential for the solubilization of the recombinant product, Casagli and coworkers studied the capacity of different denaturing agents to recover the insoluble protein aggregates. The best solubilizing agent proved to be guanidine.HCl, according to Casagli.

As the use of denaturing agents requires a refolding step to obtain the protein with the correct three-dimensional structure, Casagli and her group studied the specific renaturation conditions required for the recovery of a significant yield of soluble, active immune interferon. The partially purified immune interferon in solution buffer containing 2M guanidine.HCl was submitted to a refolding procedure by gradient dialysis or by dilution with a buffer without denaturing agent. In both cases, these investigators obtained a yield of total protein from 50 to 70 percent in relation to the initial protein concentration, with a very good recovery of specific activity. Casagli pointed out that the duration of the entire process must be controlled to avoid the fast degradation of the recombinant protein, probably because of the presence of proteolytic enzymes.

Quantitative Characterization of Porcine Somatotropin

L.H. Garcia-Rubio, Department of Chemical Engineering, University of South Florida, Tampa, FL, U.S., reported on the progress made in the use of combined light scattering-spectral deconvolution techniques for the quantitative characterization of pituitary and recombinant porcine somatotropin. Garcia-Rubio said that the quantitative characterization of proteins is essential for the development of protein purification techniques, for the understanding of the denaturation and refolding processes and for the establishment of cause-effect relationships between the protein activity and process parameters.

In their study, Garcia-Rubio and coworkers investigated model molecules for the main chromophores contained in proteins; i.e., tyrosine, tryptophan, phenylalanine and cysteine, as functions of pH, ionic strength, and chaotrope concentration. The objective of the model representation was the identification and quantification of the spectral changes undergone by proteins during the denaturation and renaturation processes. Since the denaturation-renaturation reactions of porcine somatotropin involve aggregation processes, the effect of the combined absorption and scattering was accounted for by the use of Mie and Rayleigh-Gans theories. Garcia-Rubio and colleagues showed that quantitative information on the functional groups participating in the denaturation-renaturation reactions could be obtained. According to Garcia-Rubio, their results suggest that the local pH for the aggregates can be estimated and that standard scattering and spectroscopy techniques may be misleading when used for the assessment of the denaturation-renaturation processes if the appropriate correction are not included.

New Developments in Protein Purification

E.H. Rinderknecht, Process Recovery R&D, Genentech Inc., South San Francisco, CA, U.S., presented an overview of protein purification methods as well as discussed some new methods and problems involved in large scale purification for production of therapeutic proteins.

Rinderknecht said that one of the major challenges in the manufacture of recombinant proteins for parental use in humans is unquestionably the required purity. Both classical and high performance liquid chromatography (HPLC) methods are used to characterize the final product. According to Rinderknecht, combinations HPLC and FPLC, for example, now often allow for quick and reliable detection of not only minor contaminants but also of minute amounts of N- or C-terminally processed chains, glycosylated peptides, and modified amino acid residues. Additionally, these methods have undergone considerable development over the past few years resulting in greatly improved resolving power. However, Rinderknecht said that the preparative purification technology is lagging behind and the preparative groups constantly struggle to keep up with what the quality control people find in the product with the help of the latest analytical techniques.

Although initially developed as analytical tools, both HPLC and FPLC can be turned into powerful production methods not only for small peptides but also for large proteins and might help to achieve desired purity levels of 99.9 percent or higher even on larger scales (10 to 100 mg

of protein or more), according to Rinderknecht. However, quite a few problems have to be solved to achieve this goal (for example, support characteristics and stability; particle size versus resolution; possible changes to the product upon binding to the resin; equipment; regulatory issues; and last, but not least, costs).

Rinderknecht also mentioned reversed phase hydrophobic interaction chromatography as an aid in protein purification. He also stressed that the use of silver stain which is very sensitive can reveal impurities in the recombinant product that cannot be detected by other methods. In addition, tryptic peptide maps can also aid in detecting impurities. Rinderknecht presented some examples of products purified at Genentech such as gamma-interferon, tissue plasminogen activator (tPA), and tissue necrosis factor (TNP).

Purification of a Fusion Protein

A. Danielsson, Pharmacia LKB Biotechnology AB, Uppsala, Sweden, presented an interesting report on the purification of a fusion protein containing a repeated and immunogenic octapeptide of a malaria antigen. The studies were a collaborative project with scientists from the Department of Genetics, University of Uppsala, and the Department of Immunology, University of Stockholm, Sweden. Pharmacia has many collaborative projects with university departments, particularly at Uppsala, but also Stockholm.

Danielsson said that current efforts to develop a vaccine against human malaria have largely been focused on the use of genetic engineering techniques. One approach along this line involves the construction of genes by ligation of synthetic oligonucleotides coding for immunogenic epitopes in the parasite. Recently, the expression of a synthetic gene construct encoding four repeats of an immunodominant epitope of the *Plasmodium falsiparum* antigen Pf155 was reported by scientists from Uppsala and Stockholm. In a collaborative project, Danielsson and coworkers have purified the product, a soluble fusion protein from an *E. coli* lysate. After centrifugation, the supernatant was applied to a column containing Q-Sepharose® High Performance, a new preparative anion exchange chromatography medium (34 μm bead size) produced by Pharmacia. The fusion protein was identified in eluted fractions by an enzyme-linked immunosorbent (ELISA) assay. A new preparative gel filtration medium, Superdex TM 200 PG (34 μm bead size, Pharmacia) was used for further purification. Under native conditions, different aggregated forms of the fusion protein were separated on this column. The effect of different additives on the extent of aggregation was studied. Danielsson said that an electrophoretically homogeneous preparation of fusion protein was obtained by gel filtration under reducing conditions.

Purification of Human Pancreatic Trypsin Inhibitor (hPSTi) from Recombinant *E. Coli*

J. Paulsen, Institute for Biotechnology Research (GBF), Braunschweig, West Germany, reported on this topic. The hPSTi is an inhibitor of the protease trypsin. It has a molecular weight of 6,200 corresponding to 56 amino acids. By substitution of amino acids at positions 17 to 21, scientists at the Institute of Biotechnology Research have prepared PSTi-variants that are potent and specific inhibitors of elastase and chymotrypsin. Elastase is involved in acute and chronic inflammatory processes, especially in the septic shock syndrome.

At the Institute for Biotechnology Research, the hPSTi was produced and secreted by *E. coli* strain JM 103 carrying the hPSTi gene on the pMAMPF plasmid.

Paulsen discussed his and his group's work on different ways of downstream processing of PSTI variants from the culture broth, based, for instance, on membrane processing and chromatography including biospecific absorption.

Purification of HIV-1 gp120 Retaining Receptor Binding Activity

C. Scandella, Process Development, Chiron Corp., Emeryville, CA, U.S., discussed the excellent work carried out by him and his group on this purification procedure. In this study, gram quantities of gp120 were secreted into cell culture medium by recombinant Chinese hamster ovary cell lines (CHO). The recombinant protein migrated as a diffuse band of approximately 120 kDa in a sodium dodecyl sulfate (SDS) gel and had the same amino acid sequence as the authentic virus protein. Scandella said that the virus protein initiates the infection cycle by binding to a receptor, CD4. On the surface of the target cell, Scandella and his group used an *in vitro* assay to measure the binding of gp120 to its receptor.

Purification of recombinant gp120 by a procedure involving affinity chromatography and reverse phase HPLC yielded a preparation with roughly 10 percent of the binding activity to CD4 compared to the starting material. Scandella and coworkers then developed a new purification scheme, consisting of ultrafiltration, ion-exchange chromatography, hydrophobic interaction chromatography, and gel filtration. According to Scandella, recombinant gp120 purified by this method was pure as judged by SDS gel electrophoresis and retained full activity in the CD4 binding assay. In addition, several mutant forms of gp120 missing one or more of the hypervariable regions of the protein have been constructed at Chiron

Corp. by site-directed mutagenesis and expressed in the CHO system. These proteins are also being purified for structural studies as well as for *in vitro* and *in vivo* experiments.

Characteristics and Activities of Two Recombinant Antihemophilic Factor A Proteins

H. Van de Pol, National Center for Blood Transfusion, Les Illes, France, presented an interesting report on this topic. This was a collaborative study with scientists from Transgene S.A., Strasbourg, France. The Antihemophilic Factor A (Factor VIII) is a glycoprotein present in human plasma and functions in the middle of the coagulation cascade acting as a cofactor for factor X activation by Factor IXa.

Van de Pol said that the low concentration of Factor VIII in plasma (200 ng/ml), its apparent instability and its high molecular weight (300 kDA) has hindered considerably its purification and characterization. However, the recent cloning of Factor VIII complementary DNA (cDNA), and the expression of the complete as well as genetically engineered mutant proteins have now provided an unlimited supply of the protein independent of plasma donations.

According to Van de Pol, biological activity as well as the physical structure are almost identical for the recombinant and the plasma-derived Factor VIII. Identical activation with thrombin can be shown *in vitro* and a similar correction in bleeding time is observed if infused in hemophilic dogs. Van de Pol said that normally, proteolytic processing of the complete 300 kDA molecule generates active dimers varying in molecular size from 170 kDA to 300 kDA. Furthermore, deleting the first processing site (amino acid 1664) as well as more than 90 percent of the B domain of the molecule (amino acids 771 to 1666), generates a fully active protein which can be purified as a single polypeptide with a molecular weight of about 160 kDa. Van de Pol thinks that the absence of this nonspecific processing during purification as well as the increased activation factor of this molecule are interesting characteristics for further development.

Affinity Chromatography of Recombinant Protein

E. Hochuli, F. Hoffmann-La Roche & Co., Basel, Switzerland, presented an excellent review of this topic. He said that in recent years, several very attractive approaches to facilitate purification of recombinant proteins have been developed. The general availability of monoclonal antibodies (Mabs) has had an enormous impact on immunoaffinity chromatography. This technique involves immobilization of Mabs, raised against the proteins to be purified on a solid support. The specificity of the resulting immunoadsorbent for a single epitope makes immunoaffinity chromatography a powerful method for protein purification, according to Hochuli.

Hochuli said that the use of genetic engineering techniques has allowed the synthesis of hybrid proteins. By fusing the coding sequence of a protein of interest with the coding sequence of a polypeptide with high affinity to a ligand, a hybrid protein with an affinity tag can be produced directly with a microorganism. The affinity tag can then be used to recover the product from a culture medium or a cell lysate by affinity chromatography. It is also possible to introduce a specific cleavage site at the junction between the protein parts which enables cleavage of the hybrid molecule to yield the protein of interest free of an affinity tag. Hochuli said that he and his coworkers have developed such purification methods based upon the selective interaction between a polyhistidine affinity tag and a novel metal chelate adsorbent. Hochuli presented some examples of proteins purified at Hoffman-LaRoche using immunoaffinity chromatography and the novel immobilized metal ion affinity chromatography procedure.

BioSep Designer: Computer-Aided Design of Protein

G. Stephanopoulos, Biotechnology Process Engineering Center, Massachusetts Institute of Technology, Cambridge, MA, U.S., gave an interesting talk on the BioSep Designer. He said that during the design of a protein recovery process the first question one must ask is "will it work"? With a reasonable affirmation of the feasibility, a biochemical engineer would then pose a series of more detailed questions such as, (1) how can the purity of the product be assured, (2) what is the yield of the product, (3) how much does it cost, and, (4) how sensitive is the design to upstream changes.

Stephanopoulos said that the BioSep Designer is an intelligent system providing the human with computer-aided design support to answer the above questions. It combines process simulation with automated process synthesis to generate a set of possible protein recovery and purification designs, which are *optimal*. BioSep Designer offers (1) automatic and interactive design (2) user-friendly interfaces for protein modeling (3) accumulation of protein data (4) display of process flowsheets (5) tabulation of economic analysis (6) display of explanations, and (7) display of how the design was done, and why.

According to Stephanopoulos, the BioSep Designer has been used to carry out the following tasks: (1) initial investigation of a proposed production's economic feasibility; (2) investigation of how the selection of a host

microorganism, expression method, and proteins location in the microorganism affect the economics of protein recovery; and, (3) generate protein recovery and purification systems and, in a dialog with biochemical engineers, select the best process. Stephanopoulos said that BioSep Designer has been used by industrial companies to design the downstream processing system for twelve proteins.

Microheterogeneities in a Nuclease Produced and Secreted by *E. coli*. This subject was discussed by K. Biedermann, Department of Biotechnology, The Technical University of Denmark, Lyngby, Denmark. Biedermann presented data that she and her coworkers obtained in their studies of microheterogeneity. She said that heterogeneities of a recombinant protein can occur during the cultivation of the microorganisms and during the purification procedure. Recombinant proteins destined for pharmaceutical use have to be *pure*; i.e., impurities or inhomogeneities must not be present in the final product. Since *E. coli* is frequently used as host and secretion of recombinant proteins by means of signal peptides as a possible way to obtain an extracellular and/or periplasmic protein, Biedermann and her group decided to examine the homogeneity of an enzyme – nuclease – that can be produced by *E. coli* cells carrying plasmids encoding the enzyme and its signal peptide.

Biedermann and coworkers found that the extracellular and periplasmic enzyme, which was purified by precipitation and ion-exchange chromatography, showed microheterogeneities having enzyme activity visualized by isolelectric focusing combined with immunoblotting and blotting onto agarose-containing substrate. The formation of heterogeneities was traced back to the cell culture, and it was found that they appeared during the cultivation and in the periplasmic and extracellular product. The inhomogeneites had different isoelectric points and molecular weights corresponding to monomers and dimers of the enzyme.

Biedermann emphasized that when the enzyme, nuclease, is produced by *E. coli*, microheterogeneites are formed during the cultivation of the cells. The heterogeneities are not reomoved by general purification procedures such as ion-exchange chromatography.

Validation of Biotechnical Production Processes

R.G. Werner, Bioengineering Techniques, Dr. Karl Thomae GmbH, Biberach, West Germany, presented an informative review of this subject. Werner said that production of high molecular weight and complex proteins such as glycoproteins of human origin has gained enormous importance for replacement therapy in humans. Because of the biological synthesis of biotechnically produced pharmaceuticals of proteinaceous nature, the product quality and safety of the drug is influenced by various factors.

The correct nucleotide sequence and stability of the host cell vector system provide the corresponding amino acid sequence of the protein. The post-translational processing of the protein relies entirely on the host cell; therefore, it requires a well characterized master working cell bank and a stable production cell line. Furthermore, it must be ensured that this production cell line has no negative influence on the product quality during and beyond the usual production period.

Werner emphasized that suitable equipment for fermentation allowing a sterile production of the producing monoculture and consistent conditions required for the physiology of the producing organism are the basic requirements for the validation of the fermentation process. A constant specific productivity is one of the major criteria for the reproducibility of the fermentation process. For the validation of recovery and purification of the recombinant protein, it is necessary to examine the yields after essential process steps and purification factors for removal of contaminating proteins, nucleic acids, and potential viruses. In addition to the validation of the entire production process, reproducibilty of quality of the formulated product has to be determined by a number of protein analytical, immunological, and biochemical test methods concerning identity, purity, safety, and potency of the drug.

Purification of Recombinant-Derived Tumor Necrosis Factor by Chromatofocusing

L.S. Zhiglis, Shemaykin Institute of Bioorganic Chemistry, U.S.S.R. Academy of Sciences, Moscow, U.S.S.R., presented the studies of he and his colleagues in a poster session. These investigators used a chromatofocusing technique for purification and determination of isolelectric points (pI) of recombinant-derived tissue necrosis factor (TNF). Chromatofocusing experiments were conducted on a 0.6 x 15 cm column packed with PBE 74 or synthetic ion-exchanger on a base of macroporous silica gel chemically modified with a mixed dextran-polyethyleneamine layer. As compared with PBE 74, the composite ion-exchanger was found to be more mechanically stable and also showed lower irreversible adsorption of proteins. Comparison of chromatofocusing with column isoelectric focusing showed that both of the methods yielded highly purified TNF forms with pI of 6.10 and 6.25, respectively. According to Zhiglis, chromatofocusing on a chemically modified silica gel column is an extremely useful technique for purification of recombinant-derived proteins on a preparative scale.

An Automated Purification System for the Production of Recombinant Superoxide Dismutase

This excellent study was presented in the poster session. The work was carried out by A.I. Daniels, Process Separation Division, Pharmacia LKB Biotechnology, Uppsala,Sweden, and coworkers in collaboration with C.J. Scandella, Process Development, Chiron Corp. Emeryville, CA, U.S. According to Daniels, the production of moderate amounts of recombinant DNA products at high preset levels of purity for use in clinical trials has become a critical step in the development of new drug products. There is a clear need for a reliable automated system capable of purifying up to a kilogram of these active substances per year. The BioPilot TM system, developed from the FPLC R concept (Pharmacia), has been configured by Daniels and colleagues to produce greater than 99.9 percent pure recombinant human superoxide dismutase (SOD) in an automated three-step process. The three chromatographic steps involved are (1) desalting on Sephadex R G-25 Superfine packed at a bed height of 15 cm in a BioProcess TM glass column, BPG 100/50; (2) ion exchange on Q Sepharose R High Performance (HP) packed in a BioPilot column 35/100; and (3) gel filtration on Superdex R 75 preparative grade (pg) packed in a BioPilot column 60/600. These three steps were linked together on a BioPilot TM system and run by FPLC Manager TM software. The three steps were completed within 150 minutes, allowing up to 9 cycles per day with a yield of one gram of purified material per cycle. In order to achieve this high productivity in columns of a modest size, the new high resolution 34 u diameter bead matrices Q Sepharose HP TM and Superdex 75 pg were used.

Use of an Impingement Jet Technique for the Release of Inclusion Bodies from *E. coli*

H.P. Walliser, Ciba-Geigy AG, Basel, Switzerland, presented a poster on this technique. Walliser and his coworkers carried out the work in collaboration with P. Kramer, Dechema Institute, Frankfurt, West Germany. Using impingment jets represents an alternative mechanical cell disruption procedure. It is based on the collision of two directly opposing, highly turbulent, liquid jets of a microorganism suspension. The pressure of the feed suspension can be regulated to produce the desired jet velocities (the velocities of the streams as they leave the nozzels), consequently enabling regulation of the energy available on impact for the breakage of the cells. Machine efficiency was gauged under a variety of conditions. The system pressure required is only 25 to 30 percent of that needed in conventional high pressure homogenizers to obtain comparable disintegration results. With a system pressure of approximately 150 bar, it was possible to attain 65 percent cell disruption with 1 pass and 95 percent after 6 passes. Disruption was shown to be strongly dependent on jet velocity.

Bovine interferon inclusion bocies from these studies were analyzed using sedimentation field-flow fractionation (SFFF). By collecting fractions throughout the SFFF run and subjecting them to sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), it was possible both to identify the inclusion body peak in the fractogram and to verify that SFFF has been successful in separating the inclusion bodies from the unbroken cells. Difference.. fractograms observed with changing disruption conditions showed promise for the application of this technique to the analysis of homogenates.

Conclusion

The material presented in this focused conference covered the range of purifcation steps for recombinant proteins from the primary separation to final purification of the desired product. The presentations from European as well as U.S. scientists were of high quality. The most important problem that emerged from discussions of downstream processing is that of scaleup for commercial production that still has not been completely resolved and requires further research.

FLUID MECHANICS

A NATO Workshop: New Trends in Nonlinear Dynamics and Pattern Forming Phenomena--The Geometry of Nonequilibrium

by F.K. Browand, P. Huerre, and L.G. Redekopp. Drs. Browand, Huerre, and Redekopp are in the Department of Aerospace Engineering at the University of Southern California, School of Engineering, Los Angeles.

Although fluid mechanics does not appear in the title, the conference was definitely about fluid mechanics, and brought together approximately 80 researchers from around the world. The majority were from Europe, including a healthy-sized French contingent, but the U.S. was well represented also. The clear winner in the topic sweepstakes was Rayleigh-Benard convection. If binary convection is included, the two accounted for about 25 percent of the presentations. Other subjects discussed were: various bounded and unbounded shear flow topics, reaction-diffusion chemical systems, Taylor-Couette flows, two-dimensional turbulence, and surface waves. In general, the intent was to understand flow regimes well above the critical condition, where many modes may participate to induce significant spatial and temporal complexity. But there were also a variety of micro fluid-mechanics presentations (15 percent), including flow in liquid crystals, directional solidification, and viscous fingering.

The unifying theme was, of course, the mathematical underpinnings. The commonality was demonstrated here, perhaps more graphically than at most meetings, because the subject was the geometry itself. It was impressive to see so many diverse physical systems display similar patterns.

The Dynamics of Defects

Many fluid systems achieve a state consisting of a reasonably ordered (periodic) pattern interspersed with localized, structural defects in the pattern. Examples of applications included shear flows such as the free shear layer and the cylinder wake, flow in nematic liquid crystals, Rayleigh-Benard convection, and chemical reactor systems. The nucleation and characterization of defects were discussed at length. One mathematical scenario is to imagine a perfectly ordered pattern becoming unstable to a skew-varicose instability. When many modes are present, one has *phase turbulence*. The pattern may wiggle so violently that phase crests (representing vortices, in many cases) are brought into close contact. Defects are nucleated when this happens, and an equilibrium state balancing nucleation and annihilation of defects is possible. P. Coullet and his coworkers, Université de Nice, have termed this circumstance defect-mediated turbulence.

Structural defects can arise in large-aspect-ratio systems such as the cylinder wake by artificially creating variations across the span of the flow; for example, by tapering the cylinder diameter or by stepping the diameter discontinuously. In the latter case, defects are created in the vicinity of the step because of the impossibility of a perfect match (mathematically, a form of mode competition). But even with no overt forcing, defects are the natural outgrowth of the transition process in many systems (viz., the free shear layer and Rayleigh-Benard convection), although their precise origin is still open to question. The evolution equation models for defect-mediated turbulence are often not rigorous reductions of the N-S equations, and certain parameters can be varied at will in the simulations. However, the numerical results seem to display a universal property. They predict numbers of defects that are in the same range as experimental observations for such diverse cases as free shear layers and nematic liquid crystals.

What is Turbulence?

The question, "What is turbulence?" has spawned a debate that has engaged a host of experimentalists and theoreticians studying fluid dynamics. This meeting was no exception and the diversity of the participants con-

tributed to a lively interchange of ideas and points-of-view on the question. The emphasis on the geometric character of the *turbulent* state in a variety of systems provided a fertile focus that was indeed beneficial.

Overall, the workshop was a stimulating 10 days with congenial colleagues. The French were splendid hosts. P. Coullet and P. Huerre, University of Southern California, Los Angeles, and many other unnamed workers are to be congratulated. The proceedings will be published in 1989 using the conference title, NATO ASI series B, P. Coullet and P. Huerre, editors, Plenum Press, New York/London. If the written communications are relatively close facsimiles of the lectures, the proceedings will comprise a valuable, high-level, state-of-the-art description of research frontiers for many fluid systems.

MATERIALS SCIENCE

Fourth Oxford Conference on the Mechanical Properties of Materials at High Rates of Strain

by Marco S. Di Capua. Dr. Di Capua is the Liaison Scientist for Physics in Europe and the Middle East for the Office of Naval Research European Office. He is an experimental physicist on leave until August 1990 from the Lawrence Livermore National Laboratory of the University of California.

Introduction

This conference, held at the University of Oxford, U.K., from 20 through 22 March 1989 is the fourth of a series (1974, 1979, 1984, 1989). Sponsored by the U.S. Army European Research Office, and supported by the Materials Testing Group of the U.K. Institute of Physics and the Engineering Sciences division of the U.K. Institution of Mechanical Engineers, it was attended by 64 scientists and engineers from the U.K., 20 from France (including 10 from the division of Military Applications of the French Atomic Energy Commission), 16 from West Germany, 14 from the U.S., 8 from Japan, 18 from other countries in Continental Europe, 3 from Israel, 2 from the U.S.S.R., and 1 from the Peoples Republic of China (PRC). Proceedings will be published by the Institute of Physics.

The conference discussed behavior of materials undergoing rapid, nonlinear, deformations beyond elastic limits. Such deformations typically take place under the loading that accompanies automotive, bird-aircraft, projectile, and missile impacts. In these impacts, the strength of the material, which also depends on the rate of deformation, in conjunction with inertia still determines the behavior of the structure.

Increasing attention on this subject has stimulated several recent conferences: DYMAT 85 in Palaiseau (Paris), Impact 87 in Bremen, West Germany, and DYMAT 88 in Corsica. A French organization, DYMAT, has been established to promote work on the dynamic behavior of materials and their applications. References to the proceedings of these conferences appear below.

The sessions of the conference covered

- Dynamic fracture
- Void growth and ductile fracture
- Shear banding
- Experimental methods of material characterization
- Constitutive modeling and material behavior
- Numerical modeling
- Microstructural effects at high rates of strain
- Impact and dynamic fracture of ceramics
- Impact of composites
- Impact and dynamic plastic response of structures
- Aerospace applications
- Nuclear industry applications

A detailed report on every paper presented at the conference would overwhelm the reader and detract from the value of this overview. The headings of this report reflect some of the session topics, and only some of the papers are mentioned. I hope readers and conference participants will understand.

Dynamic Fracture

Theoretical papers in the subject of dynamic fracture discussed three-dimensional solutions for stress and displacement fields associated with cracks in plates subject to dynamic loads (F. Benitez, Sevilla Engineering School, Spain) and a moving singular element method to predict energy release in fast crack propagation (W. Jian, Northwestern Polytechnic, Xi'an, PRC).

The discussions on dynamic fracture emphasized the processing of the material during crack formation as the material

- Undergoes elastic deformation
- Enters the plastic deformation region in the vicinity of the tip of the crack
- Heats through p dV work (i.e., the integral under the stress/strain curve)
- Heats locally at shear bands formed in the vicinity of the crack propagating front
- Exits the crack region and forms the lips of the cleaved material

Theorists underscored the difficulties in finding reliable measurements of local stress, local strain, and temperature fields to verify the modeling processes.

Void Growth and Ductile Fracture

I. Fyfe, University of Washington, Seattle, introduced a micromechanical description of dynamic fracture that includes the role of

- Nucleation of dislocations
- Coalescence of voids and microcracks
- Shear banding
- Necking
- Ultimate failure

His approach is to combine many of these mechanisms into a unified description of material failure. Fyfe uses failure maps, which plot damage (or plastic strain) versus a stress parameter (Follansbee, 1989).

M. Merzhievsky, Lavrentyev Institute of Hydrodynamics, U.S.S.R., echoed some of these viewpoints, introducing the relaxation time of shear stresses in determining material failure at high strain rates. This relaxation time arises from the growth rate of dislocations in the material (see Follansbee's paper below).

C. Fressengeas, French National Research Council, University of Metz, France, proposed a necking instability as the reason for breakup of shaped charged jets. In nonlinear plastic flow necking reduces the cross section, increasing the stress, and increased stress stretches the necked region, which reduces its area further. According to Fressengeas, the dynamics of the instability favors specific wavelengths, thus leading to breakup in segments. However, lateral inertia and a strong rate dependence can stabilize the flow.

E. Hirsch proposes a different breakup mechanism (Hirsch, 1989) in which the plastic velocity, defined as the square root of the ratio of yield stress to density, plays th critical role (Hirsch break-up time model).

N. Fleck, University of Cambridge, U.K., presented some new experimental stress (tension, shear, and compression)-strain curves for polycarbonate at high rates of strain for a range of temperatures. According to Fleck, polycarbonate response follows nonlinear viscoelasticity until yield, strain softening, strain hardening, and failure. Shear bands develop in torsion and compression while necking develops in tension. Above 140°C the material behaves as a viscous liquid.

H. Couque and J. Langkord, Southwest Research Institute (SRI), San Antonio, Texas, summarized recently published results, obtained with a novel (Gourdin, 1989) technique, on the transition from ductile to brittle failure of tungsten alloys, emphasizing quantitative micromechanical modeling to explain the experimental results. The results showed that the transition from ductile to brittle failure is accompanied by an increase of cracking along tungsten/matrix and tungsten/tungsten interfaces.

Shear Banding

Shear bands are regions of intense, localized slip that occur along continuum defined directions in materials undergoing plastic deformation. These bands that can form in materials deformed in compression as well as in tension and torsion, generally lead to rapid failure of the material (Follansbee, 1989).

In a session devoted to shear bands, Y. Bai, Institute of Mechanics, Chinese Academy of Sciences, Beijing, discussed the stable evolution of a shear field into shear bands. In most shear band models, the balance of the input plastic work rate and the heat diffusion governs the evolution of the band-like structure. The evolution of shear bands from the microstructure, and the reasons for a fracture surface always parallel to the shear force are not yet understood. Bai suggests that crystallographic slip leads to microscopic shear bands and that stress concentrations arising from dislocation pileups at grain as well as phase boundaries initiate microcracks that lead to material failure.

T. Wright, U.S. Army Ballistic Research Laboratory, Aberdeen, Maryland, discussed a thermoviscoplastic model where temperature perturbations trigger the formation of a shear band that often behaves as a boundary layer with a well-defined, calculable spatial distribution.

K. Staudhammer. Los Alamos National Laboratory (LANL), presented measurements of shear bands on Ti loaded at strain rates of $1.0E+06S^{-1}$ and S. Timothy, University of Cambridge, now at ALCAN International, U.K., showed metallographic sections of shear bands formed under compression by projectile impact on Ti alloys.

Experimental Methods and Facilities

Several sessions of the conference included experimental papers. I highlight presentations from several sessions on diagnostics techniques as well as facilities. Experimental papers on crack growth discussed a co-

parison of quantitative measurements on the initiation and propagation of ductile cracks (H. McGillivray, Imperial College, U.K.) and measurements of heat formation during fracture (A. Kobayashi, University of Tokyo and A. Rosakis, California Institute of Technology).

Y. Morimoto, Osaka University, described a PC-based system to analyze displacements with a framing camera that incorporates a medium-resolution, high-gain, MOS-type, solid-state sensor supplied by the same Hitachi laboratories that are developing *film-less* electronic photography hardware. Morimoto demonstrated the extensive spatial Fourier analysis (Moire patterns) features of the software by distributing a Moire-picture business card (translucent reading grid included) where grid repositioning revealed alternating positive and negative images.

R. Genussov, from Imperial College, described a clever method to apply a step load to a specimen that avoids (inward) propagating waves. A brittle material, connected in parallel with the specimen, breaks. The break suddenly transfers the full load across the specimen. He investigated crack propagation in polyethylene for pressurized piping applications. He modeled the fracture with a dynamic finite element code that includes node release along the crack path either through a decaying holding-back-force (see Merzhievsky above) or release according to experimental crack propagation data.

Experimental facilities included:

- Elegant simulation technique to visualize impact deformations (Reddy, Manchester). The target is a hexagonal close-packed assembly of rings that deform under impact. This technique has an enormous potential to simulate the behavior of solids under 2-D deformation. It reminds me of the bubble simulations of dislocation growth that R. P. Feynman (1964) discusses in "The Feynman Lectures of Physics"
- Electromechanical biaxial testing device at Ispra, Italy (C. Albertini)
- Computer controlled disk-impact machine at Stuttgart (K. Kussmaul)
- Hopkinson bar that applies multiaxial loading at high rates of strain (Fraunhofer Institute for Material Research, Bremen). K. Stiebler displayed yield loci (in the axial stress-shield stress plane) obtained in this facility
- New, electromagnetically augmented, hypervelocity impact light gas gun facility at British Aerospace-Sowerby (D. Dixon).

Constitutive Relations

Numerical calculations require constitutive relations (mechanical equations of state) that universally describe the strain as a function of stress and of temperature. The strain, not being a state variable, depends on path, thus causing almost insurmountable difficulties in equation-of-state formulation.

J. Harding, University of Oxford, introduced the main approaches to the formulation of constitutive relations. One approach is to justify functional relations on the basis of a physical model. Test data provide the constants to complete the relations. Practice shows that simple semi-empirical relationships are adequate for computer modeling of many impact problems. However, in situations where the impact response critically depends on internal microstructural states, local phenomena, and the dependence of the plastic flow on the previous strain history, empirical equations have little predictive value.

A second, very ambitious approach, developed by J. Klepaczko (1988) over the last few years, incorporates the kinetics of plastic flow. It assumes that the current mechanical properties of a material depend entirely on its microstructure. According to Klepaczko, five state variables define the state of the microstructure. The differential equations governing these state variables in turn incorporate dislocation densities, grain diameters, distance between twins, stress, and temperature. The problem then becomes to characterize the evolution of the microstructure as the material undergoes deformation.

A third approach is a simple fit of the form:

$$\dot{\Omega}^{-\alpha}\,\ddot{\Omega} - A = 0$$

first proposed by Fukuzono, that Voight (1989) elaborates upon in a recent article that was not part of the conference. Ω represents a measurable variable such as the strain and A and α are constants determined experimentally. Materials can include metals, polymers, concrete, soil, rock, or ice. *Science* is an unusual forum for this subject, so I take advantage of *ESNIB* to call it to the attention of the community.

P. Church, U.K. Royal Armament R&D Establishment, Ft. Halstead, U.K., discussed constitutive relations applicable in the numerical modeling of explosively formed projectiles. He compared the Zerilli-Armstrong (ZA) model (1987), that describes material behavior at high rates of strain based on dislocation mechanics, to empirical models incorporating strain hardening and thermal softening. Both models gave similar results even though the ZA model still needs refinements to incorporate shock hardening, twinning, and recrystallization that are, according to Church, important phenomena in the formation process of EPF's.

P.S. Follansbee, LANL, discussed constitutive relations based on internal state variables (Follansbee, 1988). An understanding of the kinetics of dislocation glide, strain hardening through accumulation of dislocations in face-centered cubic (FCC) and body-centered cubic (BCC) solids, and dynamic recovery allows the formula-

tion of the yield stress as a function of the underlying kinetics and the threshold stress that characterizes the interaction of dislocations with obstacles in the lattice. The kinetics of the interactions is a function of strain rate and temperature. The constitutive relations apply to FCC metals, where dislocation-dislocation interactions provide the thermally activated contribution to the flow stress and to BCC metals where dislocation motion is hindered by the Peierls barrier.

A paper by P. Armstrong, LANL, read by Follansbee, elaborated on the form of the relations in a companion paper and discussed their application to the deformation of alpha-uranium. He emphasized the experimental difficulties preparing samples that are free of microstrain. Alpha-uranium, because of its orthorhombic crystal structure, develops large textures, and deforms plastically as it cools.

W. Gourdin, Lawrence Livermore National Laboratory (LLNL), Livermore, California, described measurements of flow stress, strain, and strain rates in current-carrying rings expanding under self-magnetic forces to obtain constitutive properties at high rates of strain. Gourdin's results show a large decrease in the flow stress of copper with increasing grain size (Hall-Petch relationship). Comparison of his data with Follansbee's model shows a reasonably good agreement except for the larger grain sizes which Follansbee believes he can explain (Follansbee, 1989).

Experimental data on the effects of grain size and strain rate on the tensile flow stress of copper were also presented by D. Lassila (LLNL) and D. Parry (Loughborough University of Technology, U.K.). The data of both authors confirm the independence of the Hall-Petch parameter on strain rate (1.0E-03 to $5.0E+03 S^{-1}$), temperature (20 to 600°C) and strains as large as 0.2.

Numerical Modeling

The numerical modeling session got off to a good start with the presentation of R. Corran, Rolls Royce, U.K., on numerical modeling of dynamic plasticity. He presented, within the time allotted, a very comprehensive overview of software for numerical modeling of dynamic plastic deformations. However, contributions to this session were sparse due to noshows. Y. Leroy, formerly of Brown University, Rhode Island, now at Shell International Petroleum, Holland, talked about a finite element method proposed by Ortiz to study shear band formation in rate-dependent as well as rate-independent solids under dynamic loading. This method incorporates an extra mode of deformation that carries a strain discontinuity in the strain interpolation. S. Segletes, Computational Mechanics Consultants Inc., Towson, Maryland, submitted an abstract about the 2-D explicit Lagrangian code, ZEUS, designed for impact phenomena. The AUTODYN commercial software (Century Dynamics, Oakland, California) was demonstrated during the refreshment periods on an IBM-compatible PC. Descriptions of the innards of the code were sparse.

The consensus is that calculational techniques are well established. However, the community requires predictive constitutive equations, comparisons of predictions with experiment, and benchmarking of calculations to afford reasonable comparisons between codes.

Ceramic Behavior at High Rates of Strain

As painted by C. Ruiz, University of Oxford, U.K., the study of ceramics under impact is at a very early stage and pictures of their behavior are just beginning to emerge. Z. Rosenberg, Rafael Center, Israel, provided some insights by describing the role of the mechanical impedance of the phases that form in ceramic materials. Shock-induced differential displacements, arising from differences in mechanical impedance, produce cracks at the boundaries between phases. The rise-time, magnitude, and duration of the stress pulse, determine crack formation. Rosenberg bases his model for ceramic failure on this physical description and finds the threshold stresses for crack formation in agreement with measurements in the shocked specimen.

J. Field, University of Cambridge, U.K., presented experimental data, from projectile/ceramics interaction experiments, on the failure mode of ceramics, damage to the projectile, and the kinetics of impact. He accelerated steel projectiles to velocities as high as 1 kms^{-1} with a light-gas gun and determined that the relative hardness of projectile and target are of great importance. Soft ceramics exhibit shock-wave-induced failure and do not deform the projectile. Hard ceramics deform the projectile, consuming a large amount of projectile kinetic energy in the process. In Field's experiments, fracture occurred in a single plane absorbing little energy in the process.

C. Ruiz. University of Oxford, U.K., emphasized the high ballistic efficiency of ceramics when failure produces a large number of fragments. The large aggregate area that results from the fracture absorbs the projectile energy. The natural question is, then, whether one can tailor the ceramic so it breaks in a large number of pieces under impact.

Other papers discussed the impact load testing of ceramics (Cermets), (J. Duffy, Brown University); characterization of boron carbide ceramics infiltrated with aluminum and an intriguing abstract by J. Lankford (SRI) which mentioned dynamic fracture of ceramic-fiber-reinforced ceramics.

Composite Materials at High Rates of Strain

The keynote paper by G. Dorey, U.K.'s Royal Aerospace Establishment, Farnborough, described the bewildering array of phenomena occurring in composites under impact. Curiously enough, the very anisotropies that make these materials useful cause enormous difficulties in their characterization by constitutive relations. Dorey clearly identified the microstructural physical phenomena that take place during composite impact:

- Stress (tension, compression and shear) in the matrix
- Stress in the reinforcement
- Stress at the matrix/reinforcement interface

According to Dorey, when equilibration times are sufficient, the damage produced by impact loading is quite similar to that caused by static loading. Under impact conditions new failure modes arise--as fracture of the matrix and separation of the matrix and fiber phases (delamination). These failures are very difficult to predict and in critical applications, full-scale simulations have almost always been necessary.

N. Beaumont, Etablissement Technique Central de l'Armenent, Arcueil, France, introduced a model for impact on composites based on nonequilibrium thermodynamics while I. Gilath, Soreq Nuclear Research, Center, Israel, (abstract only) discussed measurements of energy densities required to damage the matrix material (epoxy), and to damage the matrix as well as the reinforcement. Gilath produced the controlled-geometry-model composites with a new method developed by Wagner et al. (1988).

J. Harding, University of Oxford, reported a marked increase of the failure strength, a moderate increase in elastic modulus, a moderate increase in failure strain at large strain rates in composites for tension and compression loads applied along the principal direction of reinforcement.

B. Parga Landa, Universidad Politecnica de Madrid, presented an elegant model to predict the impact behavior of composites in which she assumes that debonding occurs upon projectile impact. Consequently, deformation waves propagate independently through the matrix and reinforcement. This model allows simulation of the penetration process using shorter computer times and its predictions fairly well match experimental values.

In separate papers, I. Crouch, and Y. Xia, University of Oxford, discussed the perforation of layered materials and emphasized the role of the ductile phase (aluminum) in the formation of a plug arising from the tensile stretching and shearing of the aluminum phase, which are also accompanied by delamination from the matrix. These processes can be incorporated in a model to predict failure of these materials.

No composite session would be complete without a discussion of the most ubiquitous composite material--wood--one of the subjects in a recent book (Gibson, 1988). The recent rediscovery of wood, as an energy absorbing material (in casks for transport of nuclear waste, for example), requires quantification of the its dynamic response under high-rate loading conditions. Research by S. Reid (University Manchester, U.K.) is a welcome step in this direction.

Conclusions

My assessment of the field at the end of this very successful meeting is:

- Basic approaches for predictive constitutive relations exist. According to Gourdin, the field now requires data that covers a broad enough range of the relevant variables to convincingly validate models derived from them.
- Some progress has been made for simple, homogeneous, single-phase systems.
- Description of mechanical behavior, particularly under impact loading, for multiphase as well as composite systems requires substantial physical insight.
- Numerical modeling is well established as an a-posteriori analysis tool. However, according to Follansbee, process-dependent constitutive relations for deformation and fracture will likely require a new generation of codes and perhaps even computers!
- Confident a-priori predictions require process-dependent constitutive relations for deformation and fracture which apply to materials undergoing microstructural changes. Is it practically possible, therefore, to formulate a path-dependent constitutive relation and to incorporate it in a practical numerical model?
- Progress requires a transition of laboratory work from rote testing, to experiments that yield insights on physical processes.

Conference Format Remarks

This conference had a novel format, common to some International Atomic Energy Agency (IAEA) conferences. The keynote speaker in each session was tasked with reviewing the field, placing the papers of the session in context. Short ($\sim$ 5 min), oral presentations of research papers followed his presentation. The invited speaker was also a moderator during the discussions that followed the last paper in the session. Poster presentations concurrent with the refreshment breaks complemented the oral presentations. Two-page summaries of the papers (both sides of the page in the abstract book) that included key parameters and figures, were very useful to follow the presentations.

In my opinion, this format has an enormous potential since the keynote speaker can rapidly focus on key issues in the field. However, success depends on

- The effort exerted by the keynote speaker to absorb the papers in the session
- The effort exerted by the authors to deliver usable manuscripts to the keynote speakers (a mixed performance according to Dr. Harding from Oxford, the conference chairman)
- The efforts of the authors to prepare concise presentations with strong conclusions (mixed results as well!)

Perhaps, rapidly spreading facsimile machines will allow this conference format to achieve its full potential--given a natural tendency for results to materialize on the eve of departure to the meeting.

Notwithstanding these minor shortcomings, this well-organized meeting was extremely stimulating and successful.

Acknowledgements

The author thanks J. Harding, P. Follansbee, W. Gourdin, and Z. Rosenberg for comments on this report. However, responsibility rests entirely with the author.

References

Impact 87, Proceedings by: DGM Informationsgesselschaft, Obersursel, West Germany (1987).

DYMAT, Etablissement Technique Central de l'Armement, 16 bis Avenue Prieur de la Cote d'Or, 94114 Arcueil, France (Telephone: 33-1-4239618)

DYMAT 87, Proceedings, in Journal de Physique, C5, 8, Vol. 46, (1985).

DYMAT 88, Proceedings, in Journal de Physique, C5, (1988).

Follansbee, P. S. et al., Acta Metallurgica, Vol. 36, (1988), 81.

Feynman, R. P., The Feynman Lectures on Physics, (Reading, Massachusetts: Addison-Wesley, 1964).

Follansbee, P., private communication (1989).

Gibson, L. J., Cellular Solids, (Pergamon Press, 1988).

Gourdin, W., private communication (1989).

Hirsch, E., "The Mott Fragmentation Model and the Vpl Break-Up Parameter," Propellants, Explosives, Pyrotechnics, (1989), in press.

Klepaczko, J. R., DYMAT 88 Proceedings, in Journal de Physique, C5, (1988).

Voight, B., "A Relation to Describe Rate-Dependent Material Failure," Science, Vol. 243, (1989), 200-203.

Wagner, D. H. "Statistical Concepts in the Study of Fracture Properties of Fibers and Composites" in: Application of Fracture Mechanics to Composite Materials, ed. R. B. Pipes and K. Friedrich, (Amsterdam: Elsevier, 1988).

Zerilli, F. J. et al., Journal of Applied Physics, Volume 61, (1987), 1816-1825.

International Conference on Interaction of Steels with Hydrogen in Petroleum Industry Pressure Vessel Service

by Ralph W. Judy. Dr. Ralph W. Judy is an Associate Superintendent at the Naval Research Laboratory, Washington, D.C.

Under the primary sponsorship of The Mate.ials Properties Council, Inc., this conference on hydrogen in steels was held in Paris, France, 28-30 March 1989. Cooperating sponsors were The American Petroleum Institute, Association Francaise des Ingenieurs en Appareils a Pression, Creusot-Loire Industrie, Institut Francais du Petrole, Pont-a-Mousson SA, and Societe Francais de Metallurgie. The theme of the conference was the materials and mechanics technologies that support the design and safe operation of pressure vessels and piping for service where large amounts of hydrogen are present at high temperatures. Rather than emphasizing fundamental research issues, the presentations and discussions were very practical. To its credit, the Materials Properties Council has done much to organize the engineering efforts by sponsoring technical programs and by collecting and disseminating data and analyses.

Of the approximately 130 registered participants, most were from the European Economic Community countries and represented the petroleum refining industry and steel suppliers and fabricators.

The format of the conference was an opening plenary session with two keynote papers and a report from the major sponsor on committee activities, followed by two simultaneous sessions. Both keynote papers were reviews of current technology for dealing with hydrogen-assisted cracking and steels for service in hydrogen environments. Both keynote papers also raised the issues of integrity of vessels and piping; the catastrophic results of past pressure vessel failures; the difficulties of developing adequate test and analysis methods to understand the effects of hydrogen in steels; and methods to design and operate safe vessels for significant service lifetimes. The difficulty of the problem stems from the mobility of

hydrogen, and the devastating effects of hydrogen in small amounts (a few ppm) to cause drastic changes in the mechanical properties of steels. When one considers that pressure vessels in petroleum refinery service are operated at elevated temperatures while containing high pressure hydrogen for long periods of time, the seriousness of the problem becomes apparent. One recent failure of such a vessel in a refinery killed 17 workers and caused an extensive fire. The failure was attributed to saturation of the steel with hydrogen, which apparently was dissipated after the source was removed. From that experience, one could conclude that some effects are either reversible or transitory, which is a further complication.

After the opening plenary session, the conference proceeded in two simultaneous sessions. One session dealt with higher strength steels for hydroprocessing vessels, and essentially reported on compositional variations of CrMo steels. Another dealt with practical problems of hydrogen-assisted cracking (HIC), which includes blistering, scaling, and stepwise cracking of vessels and linepipes in service where the principal environmental agent is wet H2S.

On the second day, one session was devoted to testing for hydrogen embrittlement susceptibility. In this session, the need was well demonstrated for unifying the experimental approaches to understanding the behavior of hydrogen in steels. The other session dealt with variables influencing sulfide stress cracking (SSC) and HIC of steels, and emphasized using surface treatments and films to mitigate the effects of hydrogen by shielding the base material.

The final day was devoted to effects of hydrogen in thick-walled vessels and methods to determine the fitness for service of linepipe steels.

The conference closed with a roundtable discussion of the problem areas that had been raised in the presentations.

- Hydrogen affects steels in two principal ways. One is chemical attack of carbides by hydrogen to produce methane at these sites. Long-term exposure causes formation of voids, which grow to the point where mechanical stress can cause them to link, leading to blistering and scaling, or to failure at stress levels well below the predicted level. Another effect is an apparent dimunition of the mechnical properties of the steels. The defense against such attack is using alloying elements that form stable carbides, mainly chromium; hence, CrMo steels or variants of them are the most popular materials for such service. A long-standing design method to ensure operating conditions that are safe for hydrogen is the use of "Nelson Curves". These empirical curves, which are plots of allowable temperature versus hydrogen partial pressure for steels of given compositions, have been successfully used for many years to ensure the safe operation of pressure vessels in hydrogen service.
- The second degradation phenomenon is the action of the hydrogen to enhance the propagation of small cracks and other defects under static or fatigue loading mechanics to measure threshold conditions for the onset of such attack and the degree to which the resistance to ductile tearing was reduced were the subject of many of the papers presented in the conference. There are several postulated mechanisms for cracking, including HIC, stress-oriented hydrogen assisted cracking, SSC, and stress-corrosion cracking. Experimental difficulties were present at the time of the test, precisely where it was and the mechanism(s) involved in hydrogen damage. The conference dealt predominantly with these issues and their ramifications for pressure vessel safety.

In my view, the problems being addressed are formidable and the consequences of error are catastrophic. For these reasons, very conservative rules govern the design and operation of pressure vessels and piping where hydrogen is known to be present. The slow strain rate test method for defining KIH, the threshold for hydrogen cracking, is preferred by most investigators as the method for characterizing the effects of hydrogen. Considerable work was also reported on the ability of hydrogen to reduce resistance to ductile crack extension, with the characterization parameter being either J-Integral or CTOD. The principal obstacle in all of these experimental efforts was the need for means to reliably and confidently establish the location, amount, and role of the hydrogen in the test specimens. Certainly, there is a lot to be learned concerning fundamental knowledge of the behavior of hydrogen in steels; and, the situation in the engineering arena is scarcely better.

MATHEMATICS

The European Centre for Research and Advanced Training in Scientific Computation, Toulouse, France

by Richard Franke. Dr. Franke is the Liaison Scientist for Mathematics and Scientific Computing in Europe and the Middle East for the Office of Naval Research European Office. He is on leave until September 1989 from the Naval Postgraduate School, Monterey, California, where he is a Professor of Mathematics.

The European Centre for Research and Advanced Training in Scientific Computation (CERFACS) was created in February 1987 by a group of eleven French organizations and institutions. The center was conceived after a lengthy analysis of the computational requirements in various scientific and engineering fields. Goals of CERFACS are to (1) conduct research for the optimum use of the new generation of high performance computers with parallel architecture, and to (2) offer advanced training in scientific computation to European researchers, scientists, and engineers. The organization of CERFACS is around research teams, each consisting of a team leader, one or two senior research scientists, two postdoctoral fellows, and two or three doctoral fellows. The doctoral fellows work at CERFACS, although in some cases it is desirable for them to have an external advisor. It is planned that CERFACS will be a dynamic organization that will have few (or no) permanent scientific employees. The team leaders and senior research scientists are on loan to CERFACS by members of the organizing group, their permanent employers. In addition, CERFACS is anxious to have both short- and long-term visitors, supported by either CERFACS or another scientific organization. Visitors may work with an existing team, present new research themes related to the existing ones, or do high level teaching in their own field.

While the organizing entities are French, the participation in CERFACS is European, and the list of sponsoring organizations will be expanded to include other European countries. This will enable an expansion of the number of themes for research. On the other hand, CERFACS will not expand beyond about 70 scientists so the the group will remain small enough to allow interaction across all fields of research conducted at CERFACS. At the end of 1988, there were 42 scientists supported by 2 administrators. The administrative staff will remain small even as CERFACS grows.

Because CERFACS will be a training facility in the use of new computer architectures as well as a scientific research organization, access to a variety of the newest computers is necessary. Computers available at CERFACS include a ETA-10P, a Matra X-MS 7020, a GOULD NP1, and an Alliant FX80. Machines available by remote access include a CRAY-2, a Cyber 205, IBM 3090's, and an Intel iPSC/2 hypercube. Discussions are underway regarding acquiring a Connection Machine and a BBN Butterfly.

The three initial areas of research were parallel algorithms, real flows, and instabilities and turbulence. During 1988 and 1989, the areas on visualization and postprocessing, and parallelism and fundamental applications will be phased in. The strong connections between these five topics were planned from the outset. I will discuss some ideas and work being conducted on the five topics in varying detail.

Parallel Algorithms

The parallel algorithms group is under the direction of Iain Duff, Harwell Laboratory, U.K., who is at CERFACS part time. I discussed the work of the group with Dr. J.-C. Dunyach, the senior scientist. There is a significant effort on computational kernels for various computers. Linear algebra is a basic area for development, and use of the Basic Linear Algebra Subroutines (BLAS) is standard. These are available as BLAS 1,2, and 3 being vector-vector, matrix-vector, and matrix-matrix operations, respectively. Developments in solutions of equations using LU decomposition, multifrontal methods, and conjugate gradient methods have been studied (see Dayde and Duff, 1988; Duff and Meurant, 1988; and Amestoy and Duff, 1988). The results of studies by Dayde and Duff show that on the ETA-10P, the CRAY-2, and the IBM 3090/200VF the use of tuned assembly language

versions of the level 3 BLAS allows portability of block Gaussian elimination programs with little efficiency sacrifice. Comparisons were made between the performance of the machines using level 2 and 3 BLAS in Fortran, vendor-supplied assembly language versions, and tuned assembly language versions. These results were obtained using one processor; and, the results of multiprocessor versions are reported in (Dayde and Duff, 1989).

Dunyach has been working on the assembly of finite element matrices in parallel. This is an almost perfectly parallel process over the elements in the discretization; however, in practice, it requires a lot of memory references. The Alliant FX80--a shared memory multiprocessor machine--obtains a speedup of about 7.5 with eight processors since there is little contention for a channel to the memory on this machine. As an example, a problem from Aerospatiale that took 15 minutes for assembly of the matrix on one processor of the Alliant took 2 minutes with 8 processors. On the CRAY-2 with multiple processors, the speedup is not so good because the machine has only one channel to the memory.

Real Flows

The real flows group is under the direction of Arthur Rizzi, FFA, Aeronautical Research Institute of Sweden, in collaboration with Hieu Ha Minh, Institut National Polytechnique de Toulouse. The group goal is the generation of large codes for aerodynamic analysis. These include automatic generation of meshes for real aircraft geometries (in two and three dimensions) for finite element codes used in the numerical simulation process. Both Navier-Stokes and Euler equation models are being developed for modeling boundary layers, turbulence, and shocks. Their primary interest is in unsteady flows. I saw a demonstration video of a calculation of flow past a cylinder. Initially seeming to be symmetric, a slight asymmetry soon resulted in a periodic shedding of vortices off the top and bottom of the cylinder. These calculations were a result of work done by Magnus Bergman. Stephen Wornom, NASA Langley Research Center, Norfolk, Virginia, has been investigating the unsteady flow over a rectangular cavity using the CRAY-2 in a multitasking (multitasking means using multiple cpus on the same task) environment. The code has the capability of running supersonic or subsonic flow, and L/D for the cavity is an input value. A video with color coded entropy was generated by the CRAY-2.

Instabilities and Turbulence

This team is under the direction of Maurice Meneguzzi, CNRS/CEA, Saclay. The group goal of the is to develop large pseudo-spectral codes in fluid dynamics in order to use them as numerical laboratories to study hydrodynamic instabilities, transition phenomena, and fully developed turbulence. Previous work by Meneguzzi and others has been to investigate the dynamics of freely decaying two-dimensional turbulence (see Brachet, et al., 1988). This work is being extended to three dimensions using the CRAY-2 computer at the CCVR computation center at Ecole Polytechnique, Palaiseau. This computation is on a 300x300x300 grid, just permitting the calculation to be carried out in the 256 MW central memory of the CRAY-2. This calculation will be continued to a very long simulation time, and is being done at the rate of 3 cpu hours per day, after which the results are saved on 3 minicassette tapes. Enough computer support on the project, is available for some 300 hours of cpu time.

In another project, Chantal Staquet has been investigating a stratified shear flow problem. The two three-dimensional flows with different densities (lightest on top) began with a slight variation in their velocities. Experiments have shown that vortices form, combine, then break up. After the breakup, slender blobs are formed, which then once more form (smaller) vortices, which combine and ultimately breakup into still smaller blobs. Previous calculations have not shown this because it has not been possible to obtain sufficient resolution to follow the smaller scale features. According to Staquet, her calculations have been the first to demonstrate the occurrence of the repeated combination of vortices, breakup, and reformation of smaller vortices. Staquet was previously at the University of Washington, Seattle, Washington, where her work was partially sponsored by ONR (Staquet and Riley, 1988).

Visualization and Postprocessing

The visualization effort is just beginning under the direction of Pierre Herchuelz, CCVR, Palaiseau. The two fluid dynamics videos cited above are useful (but straightforward) examples of visualization. The proper interpretation of the high resolution three-dimensional data obtained in the turbulence problem being solved on the CRAY-2 will be considerably more difficult (at one time, the output consists of about 500 MB of data). One objective of the group is to develop a flight simulator for exploring three-dimensional fluid flow structures. Initially this would be done for a fixed time and would allow the observer to move around through the flow field. Later stages of development may enable similar methods for nonstationary flows, perhaps through the use of artificial intelligence techniques. The problem of visualization of results obtained from scientific computation is beginning to receive a great deal of attention at various computation centers. For example, in the case of turbulent flow, it seems unlikely that contours will suffice and new ideas are needed. It will be interesting to see how this group (and

others) attack the problems of seeing what three-dimensional structures look like.

Parallelism and Fundamental Applications

In the development of CERFACS, it is intended to maintain a balance of numerics and computer science with fundamental applications. Thus, the next group will consider algorithm evolution and parallel computer architectures and their use; and it will consider other application domains. The most promising seems to be reactive flows and combustion, oceanography, and inverse methods.

Conclusion

CERFACS is an exciting place for one interested in scientific computation at the cutting edge of future technology. It is a productive mix of internationally known team leaders and senior scientists with energetic, enthusiastic postdoctoral scientists and doctoral students in a congenial setting on the outskirts of Toulouse. Access to much of the latest computational equipment is good, and as the center expands should become better. Careful expansion (approval for the addition of 10 scientists in 1989 has been given) to include personnel from other parts of Europe and perhaps the U.S. will also enhance the center, and as a training facility it should have a far-reaching impact.

References

Amestoy, P.R., and I.S. Duff, Vectorization of a Multiprocessor Multifrontal Code, CERFACS Report TR 88/3, (October 1988).

Brachet, M.E., M. Meneguzzi, H. Politano, and P.L. Sulem, "The Dynamics of Freely Decaying Two-Dimensional Turbulence," Journal of Fluid Mechanics 194(1988):333-349.

Dayde, M.J., and I.S. Duff, Use of Level 3 BLAS in LU Factorization on the CRAY-2, the ETA-10P, and the IBM 3090-200/VF, CERFACS Report TR 88/1, (September 1988).

Dayde, M.J., and I.S. Duff, Use of Level 3 BLAS in LU Factorization on the CRAY-2, and the IBM 3090 Vector Multiprocessor in a Multitasking Environment, CERFACS Technical Report TR 89/8.

Duff, I.S., and G.A. Meurant, The Effect of Ordering on Preconditioned Conjugate Gradients, CERFACS Report TR 88/2, (September 1988).

Staquet, C. and J.J. Riley, "On the Velocity Field Associated with Potential Vorticity", Dynamics of Atmospheres and Oceans, to appear, 1988.

A Mathematician's Perspective on Trondheim University and SINTEF, Trondheim, Norway

by Richard Franke.

My visit to Trondheim was organized locally by Professor Syvert Nørsett, of the Mathematics Department, and Dr. Bjørnar Pettersen, head of the Computing Center. The university (more particularly NTH, the Norwegian Institute of Technology, which became a part of the university in 1968) is located near downtown Trondheim. SINTEF is the acronym for the Norwegian version of "The Foundation for Scientific and Industrial Research at the Norwegian Institute of Technology." Some of the activities of this center were described in *ESNIB* 88-08:46 (1988). Briefly SINTEF is the research branch of NTH and the two organizations have a very close relationship, with shared facilities and personnel. SINTEF has about 2000 employees, more than 1000 of whom are scientists, and is funded by research contracts as well as grants and contributions from public and private organizations. In addition, a number of private companies (spun off from SINTEF, and usually partly held by SINTEF) also are closely aligned. I will describe some of the activities of one of these companies, OCEANOR, as well as some of the activities at SINTEF and NTH.

RUNIT, the Computing Center

The primary computer at RUNIT, the computing center, is a Cray X-MP/28, which is proclaimed to be the most powerful computer in Scandinavia. It was financed by a combination of funds from NTH, SINTEF, and NTNF and NAVF (Norwegian research councils). The computer is widely available to educational and industrial organizations within Scandinavia. Preference is given to academic users and those supported by NTNF and NAVF who receive a 90-95 percent discount. About 40 percent of the usage of the Cray is by industrial users. Some of the computations carried out on the machine include reservoir simulation, seismic processing, weather prediction, ocean wave prediction, process equipment optimization, analysis and design of offshore structures, image processing, molecular dynamics simulation, and graphics and animation.

SIMa

I spoke with Dr. Karstein Sørli, head of the Section for Industrial Mathematics (SIMa). Basic software and advanced numerics support for RUNIT are supplied by SIMa. This includes day-to-day consulting, courses, post-processing support, and optimization of user programs. One of the goals of the center is to work with the users (and especially those with laboratory facilities) to use the Cray to enable them to plan experiments in a way which makes the best use of expensive laboratory equipment. SIMa also has a Scientific Visitor Program, which was initially set up for the visitors to give special courses. Applications courses have been given in fluids and heat transfer, reservoir technology, and structural analysis. Approximately 50 percent of the attendees have been from industrial organizations.

A major program at SIMa concerns postprocessing support. They have done some work on visualization of the results of scientific computation, most notably a video of an automobile crash simulation for SAAB. This was done using MOVIE.BYU, which they consider to be computationally quite expensive, although the video is impressive, with the stresses being color coded. As an aside, Sørli mentioned that SAAB engineers believed that the video revealed a (presumably minor) error in the simulation program, although to the casual observer this was not apparent. This does point out a possibly important use for visualization of scientific computation: to help debug large and complex programs. With the support of NTNF, SIMa is beginning a 3-year project in visualization. The project personnel intend to use standard graphical kernels and will use a high-performance UNIX workstation with windows. They want to obtain better animation than has been provided by MOVIE.BYU and are investigating several existing packages.

Department of Mathematics

Since I was unable to meet with Professor Nørsett because of an illness, my contact in the Mathematics Department was Professor Per Erik Koch. Koch has been working on tension splines with Professor Tom Lyche at Oslo University. Tension splines are useful for approximation of functions which have rapidly changing curvature since the tension parameter gives a way of controlling overshoot which occurs with ordinary cubic splines. Koch and Lyche have constructed a local basis for tension splines, analogous to B-splines. The algorithm is simpler than previous algorithms and allows for different tension values over different intervals and for the possibility of multiple knots. Although the construction works only for order up to $k = 4$, for $k = 4$ they are nonnegative, nonzero only over four subintervals, and form a partition of unity. As tension over adjacent intervals increases, the basis function tends to the piecewise linear function basis function, which is nonzero only over two intervals. This work (Koch and Lyche, 1989) will appear in the proceedings of a workshop partially sponsored by ONREUR.

Other work in which Koch is involved has to do with approximation in Sobolev spaces. This work (see Iserles, et al., 1988) gives a way of constructing polynomials which are orthogonal with respect to an inner product like that in the Sobolev space W_2^1, except that the part of the inner product involving the derivative is weighted. These polynomials can then be used in Fourier-type approximations of functions when it is important to approximate derivatives closely, such as spectral methods for differential equations. (The usual Fourier approximation with Legendre polynomials generally does not approximate derivatives well.) An example shows that even a small weight for the derivative term results in a much better approximation to a given function near the endpoints of [-1,1] with no discernible degradation in the interior of the interval. Further work on applications of the approximation is in progress.

Other work by Nørsett (and H. H. Simonsen) concerned parallel methods for solving (nonstiff) ordinary differential equations. This work, based on extrapolation, was carried out on the Cray computer. The parallelism was carried out by computing several steps in parallel, and accepting the largest step which satisfied the error tolerance. The extrapolation was computed in a column by column manner to make best use of long vectors.

MARINTEK, the Marine Technology Center

MARINTEK is an independent company which is partly owned by SINTEF. It is both physically and logically part of the SINTEF group, so much so that a casual observer would probably not guess it is an independent company, since it shares facilities and personnel. The laboratory facilities include a 80x50x10-meter wave tank, three towing tanks (two of which can be combined to obtain a tank 260 meters long) and two cavitation tunnels. The waves for the wave tank are generated by a computer-driven device which has the capability of producing a large variety of waves up to 0.9 m high with periods of 0.6 s or more. The facility includes a workshop with numerically controlled machines for building models, propellers, and other necessary items. There were many models up to several meters long in the shop, including several large and distinctive "hotel" ships and a catamaran ferry. During my visit, I met Al Borzoo and a team from Naval Sea Systems Command (NAVSEA) who were preparing to test a model small waterplane area twin hull (SWATH) ship in the wave tank. Mr. Knut Minsaas, the chief scientist, conducted the tour along with Dr. Pettersen. They explained that one of the goals of the center was to incorporate use of the Cray computer into all aspects of the la-

boratory, from planning of experiments and design of the models to rapid evaluation of the data obtained from the experiment, and projection of any necessary design improvements.

OCEANOR - the Oceanographic Company of Norway A/S

OCEANOR is a privately held company, partly owned by SINTEF and closely allied with SINTEF and NTH. My host there was Dr. Harald Krogstad, who is presently at SIMa but was previously employed at OCEANOR. The company employs about 75 persons.

Krogstad's work has been in calculation of ocean wave spectra from experimental data. Data obtained from an acoustic Doppler current meter during the Current Measurement Experiment (CUMEX) in the Norwegian sea was analyzed for directional wave spectra by the Iterative Maximum Likelihood Method and reported on in Krogstad, et al. (1988). Previous work in this area used the Maximum Entropy Method for data obtained from a heave/pitch/roll buoy to estimate the directional wave spectrum (Lygre and Krogstad, 1986).

I spoke with Jan-Petter Mathisen about his work in modeling ocean currents. OCEANOR has several computer programs available for modeling various aspects of ocean currents and waves. Most of their modeling is of the North Sea and Norwegian coast areas and is conducted to investigate pollution transport (e.g., fjord flushing), oil spill dispersion, fish farming, and other biological phenomena. Among the computer models which they regularly use are:

- Duchess--a 3-D model incorporating topography, wind fields, and tides to predict storm surges and currents
- Hybos--a 3-D model with a curvilinear grid which simulates water level, current profiles, and circulation from topography, wind fields, and tides
- Dolphin--a wave model for deep water using wind fields and topography data
- Hiswa--a wave model for shallow waters using data on deep-water waves, topography, and wind fields
- Difha--a wave model for harbors with wave breaking, from data about various types of construction
- Snocos--predicts wind-driven swells on the Norwegian continental shelf
- Jet--a discharge model simulating spreading from sewage outfalls and other discharges
- Slickmap--simulates drift and ultimate destination of an oil spill from a given site
- Doosim--forecasts drift and ultimate destination of an oil spill following an accident at sea
- Driftmap--simulates drift times and likelihood of oil spills from potential offshore production sites reaching shore.

In addition to the computer models, OCEANOR also has an instrumentation department to develop instruments for making ocean measurements, and a field department to perform measurements for the various departments at OCEANOR.

Øistein Johansen is working on oil spill models. These use a convection-diffusion scheme. He is now extending the models to include an ice shelf and ice chunks in the water as well. The effects of the ice chunks will be simulated stochastically. The intent is to do a number of simulations with various assumptions about wind directions and other parameters to find a percentage of spills that eventually reach a given point. Plotted contours of the probability of a spill reaching a particular point can then be used to assess the general vulnerability for a particular area. The limitations of this kind of analysis would have to be carefully explained to the novice, especially with regard to a specific incident.

I spoke with Richard Olsen about his work on processing ocean wave data. He, along with Krogstad, was involved in the Labrador Sea Extreme Waves Experiment (LEWEX). This was an international, cooperative basic research program concerned with full-scale measurements, analysis, modeling, and simulation of 3-D seas. The first phase of the program took full-scale wave measurements in the North Atlantic Ocean at a time and place that had a high probability of severe sea states. Data obtained included that from a four direction-measurement (WAVESCAN) buoys and directional sea spectra measured with an airborne synthetic aperture radar (SAR). The airborne data was taken by flying over the site in various directions and altitudes. This data was then used to compare with "hindcasting" done by 3G-WAM, a third generation wave model (see Kjeldsen, et al., 1988).

The data from the experiment requires extensive processing before comparisons can be made. For the WAVESCAN data, a directional analysis is carried out on the time series analysis obtained from rotating the pitch/roll series into the north-east reference system. The Fourier transform must be corrected by the system's transfer function (supplied by the manufacturer) and for the buoy's hydromechanical behavior, assumed to be a forced linear oscillator with known frequency and damping. One of the experiments was in the vicinity of the interface between the cold Labrador Current and the warm Gulf Stream. The strong currents in this region apparently affect the propagation of swells and must be taken into account in wave models.

Data from the SAR also must be processed, although a full understanding of all the mechanisms that must be

taken into account is not yet understood. For example, rotating particles in waves result in Doppler shifts that somewhat confound the imaging. Scene motion effects can be divided into coherent (such as velocity bunching, acceleration defocus, and coherence time limitations) and incoherent (such as scanning distortion and look misregistration) effects. For determination of directional wave spectra it is important to properly understand the scene motion effect. Work is in progress in understanding the potential for making use of SAR data. A comparison of wave spectra from the two sets of data is contained in a recent presentation (see Krogstad and Olsen, 1988).

Conclusions

The working relationship between NTH, SINTEF, and the closely aligned companies is an enviable one from the viewpoint of researchers in university, government, and industrial settings. It is a setting that I know many in the U.S. (especially at universities) would find to be very desirable from the standpoint of research ideas and support. The work being performed there in support of, and in collaboration with industry appears to be first-rate. Because of the present depressed prices for oil, growth and profitability (of SINTEF) has been held down, although the situation had improved considerably in 1987 over 1986, while 1988 appears to be a reasonably good year. When oil prices again increase I have no doubt that the research program at SINTEF will expand considerably.

References

Koch, P.E., and T. Lyche, "An Algorithm for Computing B-splines in Tension," in Mathematical Methods in CAGD, ed., T. Lyche and L. Schumaker, (Academic Press, 1989).

Iserles, A., P.E. Koch, S.P. Nørsett, and J.M. Sanz-Serna, "Orthogonality and Approximation in a Sobolev Space," preprint, 1988.

Krogstad, H.E., R.L. Gordon, and Martin C. Miller, "High-Resolution Directional Wave Spectra from Horizontally Mounted Acoustic Doppler Current Meters," to appear in Journal of Atmospheric and Oceanic Technology (1988).

Lygre, A., and H.E. Krogstad, "Maximum Entropy Estimation of the Directional Distribution in Ocean Wave Spectra," Journal of Physical Oceanography 16 (1986), 2052-2060.

Kjeldsen, S.P., H.E. Krogstad, and R. B. Olsen, "Some Results from the Labrador Sea Extreme Waves Experiment," presented in 21st International Conference on Coastal Engineering, Costa del Sol, Málaga, Spain, 20-25 June 1988.

Krogstad, H.E., and R.B. Olsen, "An Intercomparison of SAR and Buoy Directional Wave Spectra from LEWEX," in Proceedings of IGARSS '88 Symposium, Edinburgh, Scotland, 13-16 Sept. 1988.

Mathematics and Scientific Computing in Bergen, Norway

by Richard Franke.

Introduction

Bergen, Norway, is the home of two scientific research centers and a university. During my visit to Bergen, I talked with people at the Bergen Scientific Centre, the Chr. Michelsen Institute, and the Computer Science Department at the University of Bergen. Some of the research is conducted jointly between two or more of the groups, and several of the personnel at the Bergen Scientific Centre were previously at Chr. Michelsen Institute.

IBM Bergen Scientific Centre

The IBM Bergen Scientific Centre (BSC) was established in 1986 in buildings owned by the University of Bergen. The computer, an IBM 3090/200VF (scheduled for upgrade to model 400VF) is housed in one building, while another building serves as offices for scientists and administration. At the time of my visit in November, office space was at a premium, but a move to a new building was scheduled and may have been accomplished by this time.

The BSC was established in order to provide a computational research facility that would help foster and support scientific research beneficial to Norway (Gaffney, 1987). This has a very strong bearing on the types of research conducted which includes Information Technology, Reservoir Simulation and Seismic Processing, and Biotechnology and Fish Farming. Research is conducted in partnership with industrial and academic institutions in Norway, which generally provide the background expertise to formulate the scientific model of the problem, and may also contribute to the mathematical modeling of the problem. In most cases, the BSC then provides the expertise in numerical-computational modeling and software development. Collaboration continues through the postprocessing stage for accurate interpretation of the computational results.

The personnel of the BSC are an international group. Many are short-term visitors who are unable to spend long periods of time away from their home base. This gives the BSC the opportunity to respond to needs quickly and to entice visitors with a short lead time. In addi-

tion, the BSC provides office space and computer support for employees of their partners. The faculty and students at the University of Bergen have free computer use, even for projects unrelated to those at BSC.

Other activities of the BSC include teaching graduate level courses open to University of Bergen students. Courses are generally conducted by BSC visitors. The first two courses were ocean eddies and fronts, and pattern and image analysis. The BSC has also organized a recent conference on vector and parallel computing (see Blackburn) and is planning another for 1990.

Dr. Patrick W. Gaffney is the Director of the BSC. While at BSC, I talked with many of the researchers about the wide range of problems on which they work. I was impressed with the friendliness and willingness of everyone to talk about their projects.

Some Research Topics at BSC

Christopher Thompson, who joined BSC from Argonne National Laboratory, Argonne, Illinois, is responsible for the Advanced Interactive Executive operating system (AIX), a UNIX-like system from IBM, activity and for a Computational Fluid Dynamics Group at the BSC. Mr. Thompson is involved in three projects at BSC. 1) Multiprocessing: Thompson is establishing a network of AIX-based workstations, RT and PS/2 computers, to do distributed parallel processing, and is using this network to solve various problems. He has recently been working on tools for discovering parallelism in Fortran programs (see Cowell and Thompson, 1988). 2) Multigrid methods: Thompson is applying multigrid methods to steady state Navier-Stokes flows. His primary interest is in cases where there is a boundary layer and the grid must be refined in this region for adequate resolution of the problem. One example is a reactor cooling problem--the model is a tank of water, insulated on top and bottom, with a heat source on one side. There is a boundary layer on this side, and little happens elsewhere. Another example is modeling oil retrieval by pumping water into the reservoir. The action is near the oil-water boundary with little activity elsewhere. Thompson is applying multiprocessor machines to the multigrid refinement problem. 3) Time-dependent problems: Thompson is investigating the time-dependent versions of the above problems, particularly oil retrieval.

Johnny Petersen is converting SESAM/FENRIS, a commercial structural dynamics code to run on the IBM 3090 multiprocessor systems. The code is being converted to the IBM Parallel Fortran language, which aids in generating parallel code.

Petersen also has extensive experience on the Intel iPSC hypercube computer (Petersen and Renaut, 1988; De Pillis-Lindheim, et al., 1988; Petersen, et al., 1988; and Petersen and Lindheim, 1988). His experiences have been presented at professional meetings and documented in technical reports and papers, and I will confine myself to an anecdote. The one number of most interest during investigation into using parallel computers is the amount of speedup in the solution of the problem when using n processors over that when using one processor. The ratio of execution time with one processor to that with n processors is generally between one and n. Petersen and his coworkers discovered that on the Intel iPSC it is possible to get a speedup of greater than n in some circumstances because if arrays larger than 64K are used with the 80286 processor, the addressing requires additional work. If the problem is partitioned between enough processors so that only arrays smaller than 64K are needed, the total speedup can be greater than n. This phenomenon will presumably disappear with the iPSC/2 which uses the 80386 processor.

Gunnar Furnes' primary interest is ocean current modeling, but he also works in numerical weather prediction with coworker Alastair Jenkins. Their work is connected with modeling currents and surges in the North Sea and off the Norwegian coast. They use two models--a two-dimensional depth integrated model and a three-dimensional spectral model. The models run on the IBM 3090 parallel computer (Furnes, et al., 1988). They have a time history of tides, winds, and pressure since 1955. The models are used for a variety of purposes, including storm surge prediction, pollution tracking (both forward and backward in time), fish egg and other biological tracking, and to provide design parameters for offshore construction. The importance of ocean current modeling for Norway is underscored by the fact that water flows into the North Sea basin from many sources --from the Baltic Sea, from rivers, north through the English Channel, or southeast past the northern coast of Scotland; but, the only flow out of the North Sea is via the Norwegian Trench along the southwestern coast of Norway. This has potentially serious implications since pollution from many sources is then swept past the Norwegian coast. Recent calculations by BSC have been done to try to understand the factors behind the recent algae bloom that occurred in the Skagerrak Sea. Unofficially, these factors probably played an important role. Furnes has investigated how the trench affects currents (Furnes, 1987). In connection with Hamburg University, a new simulation model--a so-called layered model--will be developed and implemented. Another area is simulation of currents in fjords.The fjord current calculation models are not presently connected with the open ocean models, but Furnes intends to couple the two.

Øistein Bφe works on reservoir modeling--the flow of oil forced through a porous medium by water injection. The small scale problem is a boundary layer problem, where little happens except near the interface. Bφe has written a report on an attempt to simulate laboratory re-

sults (Bφe, 1987). The overall problem is modeled using a dual continuum model. The porous part of the medium cannot actually be "seen" by the large scale model, so that part is approximated by a filtration velocity. The purpose of modeling the small scale behavior is to attempt to determine the transfer term between the small scale and large scale parts. Ultimately, they would like to be able to determine the rate at which water should be injected for optimum oil production.

Christopher Giertsen is working on the graphical interface for the other scientists. Presenly he is conducting tutorials regarding the kinds of graphics available and examples of the kinds of things that can be done graphically, with the commercial packages available at BSC. One example was a shaded three-dimensional plot of the North Sea bottom terrain with current vectors superimposed at the surface. Another dealt with the surface currents as well as those halfway down to the bottom, but was difficult to interpret. The picture would be quite suitable if it could be viewed in three dimensions.

Jens Houlrik and Trond Aukrust are involved with several projects in computational physics. 1) Catalytic processes: The process does not work properly if the mixture is too rich in either oxygen or carbon monoxide; i.e., automobile catalytic converters. He is trying to simulate the process. 2) High T_c superconductors; They are trying to model structural phase transitions of high T_c superconductors. 3) Diffusion limited aggregation: Diffusion limited aggregation (DLA) models the aggregation of particles in a diffusion process undergoing a random walk until they are attached to the aggregation. Among other processes, the model can be applied to fluid-fluid displacement in porous media. The aggregation forms a blob with a fractal boundary. 4) Surface physics: The properties of very thin layers of silicon under varying environmental conditions; i.e., temperatures and pressures, are being studied through simulations. Some experimental results are being used to verify the simulation program. 5) Josephson junctions: The Josephson junction phenomenon between two parallel superconductors is being simulated and the material is modeled as grainy, rather than homogeneous. Experimental results are available for checking the algorithm.

Lothar Reichel is a visitor from Kentucky University, and has varied interests. (1) Toeplitz eigenproblems: The Levinson algorithm is used to find the Schur parameters. The Schur parameters lead to 2x2 Givens rotations, the product of which is an orthogonal matrix of Hessenberg form. The eigenvalues of this matrix are the Pisarenko frequencies. The algorithm parallelizes well, and Reichel is searching for situations where the scheme is applicable. This investigation and other of Reichel's work has been conducted jointly with Professor William Gragg of the Naval Postgraduate School. (2) Numerical stability of Newton interpolation: The numerical stability of the Newton interpolation formula depends on the ordering of the equally spaced nodes (in the complex plane). On the unit circle, the best ordering is related to the order in which results are returned in an in-place FFT calculation. For other configurations, it may be possible to infer results via conformal mapping. As an example of the kind of stability differences found, an increase from order 18 for the natural ordering to order about 500 in the most stable ordering is possible in single precision on the an IBM mainframe. (3) Fast solution of Fredholm integral equations: In this work, Reichel considers discretization of the integral equation by a Nyström method, resulting in a system of $N + 1$ linear equations. By Fourier analysis he shows the coefficient matrix can be replaced by a low rank modification of the identity matrix, and the resulting equation can be solved in O (NlogN) operations. Under suitable smoothness conditions for the kernel, the approximate solution converges optimally to the true solution. The same type of method also works when the underlying approximation is by a Chebyshev-Galerkin scheme, and is also considered (Reichel, 1988).

Leonard Gray is a visitor from Oak Ridge National Laboratories who works on the applications of the Boundary Element Method to various engineering problems. His most recent work is concerned with a new procedure for treating electroplating problems when shielding is present, but which also has application to crack problems. The method utilizes two equations at each node of a slit (or crack), one being the standard boundary element approximation and the other obtained from the normal derivative of the equation. This is contrasted to other techniques where artificial boundaries and nodes and matching equations are used, leading to greatly increased complexity if there are many slits. Further, the latter scheme is not easy to apply in the three-dimensional case. (see Gray, 1989 and Gray, et al., 1988). The technique does require the evaluation of what Gray calls hypersingular integrals, which are integrals that require additional smoothness of the boundary approximation for proper evaluation. He discusses a possible solution and gives results in Gray (1988). Good results have been obtained, although my observation is that this seems to be a nonconforming scheme (in the finite element sense), and that use of a C^1 boundary element is proper.

Chr. Michelsen Institute

The Chr. Michelsen Institute (CMI) was established in 1930, and presently employs about 170 persons at its facility in Fantoft, near Bergen. A basic grant is provided by the Royal Norwegian Council for Scientific and Industrial Research, with additional funding from the petroleum industry, other domestic and foreign industry, and government departments. The largest department is the Department of Science and Technology with 125 em-

ployees, the Department of Social Science and Development with 30, and Administration with 15. The Department of Science and Technology is concentrated in four main areas:

- Measurement technology and instrumentation
- Powder, dust, and gas research
- Computing
- Applied economics.

The institute's work involves both fundamental and applied research and development, as well as information and consulting services. A closely allied facility is the Centre for Petroleum Economics (established in 1979) with 20 researchers in economics and an additional ten advisors who are attached to and integrated into CMI's work.

Graphics and Visualization

My visit to CMI was arranged through Dr. Jeremy Cook, of the computing center. Cook has been working on an interactive graphics interface to large scale scientific computations. Output from the large scale machine is fed into a program and the information then displayed in any or all of several graphical windows. The pilot system runs under UNIX with SunView on a Sun workstation connected to an Intel iPSC/1 hypercube, but it should be easy to convert it to other workstation/mainframe combinations. The package is designed to serve as a general user interface. According to Cook, use of the system allows a programmer to build a specific user interface within the windowing environment in one working day, instead of an estimated 5-25 days (depending on complexity). The interface package--*win-pack* (Cook, 1988)--is written in the C language using the UNIX tools *lex* and *yacc*, but little C programming is required by someone designing a graphics interface for a new application. The applications programmer uses a definition file to specify information about the desired graphics interface. The user must define the frame, the graphics window, the control panel window, and the call back functions initiated via the mouse. These are then converted to a C program by *win-pack*. This program could then be enhanced by the programmer if desired. The programmer also supplies the necessary display routines for the data to be shown graphically.

I saw demonstrations of three different interfaces which were built using *win-pack* on the SUN-iPSC combination. 1) A seismic processing example showing a sequence of reflected waves. They were represented as a series of vertical plots with the horizontal being the intensity of the sound. 2) This example was originally designed to run on an Alliant FX-8 by Professor John Gilbert, Cornell University, Ithaca, New York.. It was a graphic display of the details of the work assignment to various processors during the solution of a sparse system of linear equations. The presentation was a tree structure that showed the sparseness structure of the matrix, and the processors work assignment progressing up the tree as the solution (LU decomposition, actually) proceeds. It is possible to slow down or stop the process to carefully inspect the current job disposition. One can easily investigate the effects of different orderings of the matrix columns. Also, this can be used as a diagnostic tool to determine if the calculation is proceeding properly or whether there is a bug. 3) This example of the graphical interface concerned the use of acoustics for fish population studies. Here the input was not from another computer, but acoustical reflections from fish in the ocean. The reflections are represented as a two-dimensional slice. The operator can scale the sensitivity up/down and, from the type of image, decide on species and number of fish. The system is ready for actual trials with the workstation aboard ship. The pilot version of *win-pack* for SUN-iPSC/2 is available. A more general package implemented under X-windows for a range of other workstations and data processor combinations should be available soon for a nominal charge. For information, contact Dr. Jeremy Cook, CMI, Centre for Computer Science, N-5036 Fantoft, Norway (telephone: 47-5-284410).

Ultrasonic Instrumentation

The other group at CMI with whom I spoke was the Ultrasonic Instrumentation group. The principal scientist is Dr. Magne Vestrheim, with 12 persons working on several projects, including ultrasonic flowmeters, seismic applications, and ice thickness measurements. The flowmeters are presently used to measure the flow of natural gas in large pipelines as well as flaregas at well sites. A company associated with CMI--Fluenta A/S--manufactures and sells the meters. The group is simulating flowmeters mathematically and computationally. Their simulation program models the various effects of the system through transducers. The input is the signal in the time domain, and outputs at various stations along the way are available, along with the transfer function at various nodes. They are adding the effects of bubbles and eventually want to model multiphase flow to develop instrumentation for measuring it.

They are also working on seismic processing. One of their primary goals here is to detect underlying structure, especially shallow gas zones (Vestrheim, et al.). They are using parametric acoustical source terms for this purpose. Two sources, close in frequency, give the sum and difference frequencies. Since they want a low frequency source, the sum frequency is filtered out. The calculations needed are not computationally intensive; Hankel transforms are the main part of the calculation. In a re-

lated effort, they are working on the development of software for pulse forming and generation for parametric acoustical sources.

The use of acoustical remote sensing to monitor polar drift ice is being investigated. For this purpose, they propose an uplooking sonar device that is placed either on the ocean bottom or on a submerged, tethered float. The instrument measures the ice drift velocity and ice thickness. The present system is designed to be retrieved in order to obtain the data, although future systems may be expendable with the data being retrieved by ship, airplane, or hydrophone (Kvinge, et al.).

Research in Numerical Cubature at the University of Bergen

Professor Terje Espelid, Department of Computer Science, University of Bergen, has worked extensively in multidimensional quadrature (or cubature, as it is sometimes called), and has most recently focused on the development of routines for automatic estimation of multidimensional integrals (a black box subroutine being the goal). Much of his work has been with Jarle Berntsen and their respective students.

The basic problem is simple. Given a multidimensional integral, its value is approximated by a sum of weighted function values

$$\int_C f(x)\,dx \approx \sum_{k=1}^{N} w_k f(x_k)$$

Here C is a region in n-space, and the x_k are called nodes, the scalars w_k are called weights in the cubature formula. If the approximation is exact for all polynomial integrands of degree d (but not degree d + 1), the formula is said to have precision d. It is desired to compute the approximate value of the integral, accurate to a specified tolerance, ε, or to find that it cannot be done with the resources available; e.g., the arithmetic precision being used in the calculation or the cost of the calculation. The subroutine would ideally be infallible, but one must settle for a tradeoff between reliability and cost.

Berntsen's and Espelid's earlier work has been preliminary to the goal of devising software for the problem. But first, in order to more easily understand the problem, I digress to discuss some basic ideas. To make practical the estimation of integrals in several dimensions, it is necessary to have highly efficient cubature rules; and, in order to simultaneously estimate the error, it is convenient to have embedded cubature rules. A pair of embedded cubature rules of different precision (typically of precision 2m + 1 and 2m-1) have the same nodes (the second uses a subset of those of the first). The difference between the two is called a null rule, and the value of the null rule gives an estimate of the error in the second cubature approximation. Depending on the shape of the region C, it may be possible (and desirable) to apply the rules to subdivisions of the region; e.g., if C is a hyper-rectangle, then C could be divided into smaller hyper-rectangles and the formula applied to each, then summed to obtain the approximation. Such a rule is called a composite cubature. These ideas are at the heart of any adaptive cubature algorithm.

When the region of integration has symmetry properties, it is useful to use cubature rules that have the same symmetry, as this decreases the effort required to find the nodes and weights in the formula. The theory of cubature in several dimensions partially carries over from one dimension; i.e., the nodes are common zeros of certain orthogonal polynomials, just as for Gauss quadratures in one dimension. However, the theory is nowhere near as satisfactory in that weights may be negative, the nodes may be outside the region C, and the number of nodes required for approximations of a given polynomial precision for a given integral is generally not known. Nonetheless, the theory is useful for easing the effort required to compute the nodes and weights of cubature formulas. Some of their recent work on construction of cubature formulas is given in Berntsen and Espelid (1988) and Espelid (1987), and on error estimation in Berntsen (1988).

The culmination of their work is a Fortran algorithm--*Adaptive Multidimensional Integration* (ADMUNT)--that calculates the value of integrals over hyper-rectangles (see Berntsen, et al., 1988, 1988a). This algorithm has been extensively tested and compared with other algorithms (see Berntsen, et al., 1988b). The results given include tests with integrals in up to 15 dimensions. Because integrals in many dimensions are very expensive to estimate, only limited testing could be done in higher dimensions.

The algorithm has the following features:

- The algorithm applies to the integral of a vector function. The algorithm adaptively subdivides the region in the same way for all vector components, based on the maximum error estimate over the components. The error estimate for subdivided regions involve an empirical formula that depends on the error estimate for the parent region to avoid losing a bad spot in the subdivision process.
- In order to make efficient use of the p processors during the subsequent calculation, region subdivision on a computer with p processors is performed for p/2 regions at each subdivision time. Near linear speedups are reported on the Alliant FX/8. For example, with 6 processors in use for a degree nine rule in 5 dimensions, a speedup of 5.17 is reported over that with the use of only one processor. The more expensive the integrand

evaluation is, the better the parallel performance will be.

- Subdivision is performed by division along one axis of the subregion to be subdivided. The axis is chosen on the basis of a fourth difference calculation in the coordinate directions, the function values involved being a subset of those used in the cubature rule.
- The basic integration rules used are families of fully symmetric rules. The precision of the rules that can be selected are 7 and 9 for all dimensions (≥ 2), with 13 and 11 being options for two and three dimensions, respectively.
- The test results indicate that ADMINT is very reliable. It is more reliable and more efficient using the higher precision rules, at least up to 6 dimensions and for high accuracy. Because of the computational expense, high accuracy experiments were not conducted for dimensions greater than 8. For low accuracy in many dimensions, it may be advantageous to use another scheme they also tested, based on Korobov rules (see Korobov), that use number theoretic ideas (see Genz for a description of the software, KROBOV). Since ADMINT is based on polynomial approximations, KROBOV is also better to use on discontinuous integrands.
- The routines have been tested on a variety of machines: Alliant FX/8, SUN 3/50, CRAY X-MP/48, IBM 3090, Sequent Balance 8000, and HP-3000/840.

Conclusions

There is a lot of scientific activity at BSC, most involving large scale scientific computation. The technical reports cited here (which are intended to be precursors of journal or proceedings publications) are but a sample of the output of BSC, and testify to the wide range of work performed there. Pleasant work conditions, agreeable and stimulating colleagues, and easy access to excellent facilities all help foster the enthusiasm that I found; all help to account for the excellent work.

The CMI embodies an interesting combination of applied research and development with a captive company able to put products on the market. In this sense, CMI is quite different from (and complementary to) BSC, which is purely an information development facility.

The quadrature work at the University of Bergen is excellent. The producing and testing of high quality mathematical software is a time consuming process, ideally performed by one intimately familiar with the numerical analysis and also familiar with good program ming practices and the design of convenient user interfaces. Too often, only one of these desirable traits exists, which results either in good software that is unused because it is too cumbersome, or bad software that is easy to use (and consequently, is often used). The work described here appears to be well designed and very useful software (I have not reviewed and tested the software itself, such as it will be before publication). While the problem of numerical integration over a hyper-rectangle is an important one, more difficult problems await resolution. Since more general regions can be broken down into unions of simplices, a more ambitious and necessary project is that of basing the cubature formulas on the n-simplex. Related work at the Catholic University of Leuven, including projected extensions to simplices in two and three dimensions, has been reported previously (*ESNIB* 89-04, pp. 19-23).

References

Berntsen J., and T.O. Espelid, "On the Construction of Higher Degree Three-Dimensional Embedded Integration Rules," SIAM J Numer. Anal. 25(1988):222-234.

Berntsen, T., Practical Error Estimation in Adaptive Multidimensional Quadrature Routines, Report 30, Department of Informatics, University of Bergen, Bergen, Norway, April 1988.

Berntsen, J., T. Espelid, and A. Genz, "ADMINT: An Adaptive Multidimensional Integration Routine for a Vector of Integrals," submitted to ACM TOMS, 1988.

Berntsen, J., T. Espelid, and A. Genz, "An Adaptive Algorithm for the Approximate Calculation of Multiple Integrals," submitted to ACM TOMS, 1988a.

Berntsen, J., T. Espelid, and A. Genz, A Test of ADMINT, Report 31, Department of Informatics, University of Bergen, Bergen, Norway, September 1988b.

Blackburn, J.F., The 2nd International Conference on Vector and Parallel Computing, ONREUR Report 9-1-C, 1989.

Boe, Ø., Application of a Time Discretized Petrov-Galerkin Method for Simulation of Laboratory Displacement Experiments, BSC Report 87/15.

Cook, J., Graphical Interface for Large Scale Numerical Computation, CMI Report 88/45055-1, June 1988.

Cowell, W.R., and C.R. Thompson, Tools to Aid in Discovering Parallelism and Localizing Arithmetic in Fortran Programs, Report MCS-P6-1088, Argonne National Laboratory, October 1988.

de Pillis-Lindheim, L., J. Petersen, and J. de Pillis, An Iterative Solution to Special Linear Systems on a Vector Hypercube, BSC Report 88/9.

Espelid, T.O., "On the Construction of Good Fully Symmetric Integration Rules," SIAM J Numer. Anal. 24(1987):855-881.

Furnes, G., J. Petersen, and B. Ådlandsvik, Numerical Sea Modelling Using Parallel Vector Processing, BSC Report 88/13.

Furnes, G., On Bottom Trapped Waves Over the Western Slope of the Norwegian Trench, BSC Report 87/6.

Gaffney, P.W., The Profile of the Bergen Scientific Center Year Ending 1987, BSC Report 87/19, 1987.

Genz, A.C., "Testing Multiple Integration Software," pp. 208-217 in B. Ford, J-C. Rault, and F. Thommaset, Eds., Tools, Methods and Languages for Scientific and Engineering Computation, North Holland, New York, 1984.

Gray, L.J., "Boundary Element Method for Regions with Thin Internal Cavities", Engineering Analysis, to appear, 1989.

Gray, L.J., G.E. Giles, and M.W. Wendel, "Boundary Element Method for Regions with Thin Internal Cavities II," submitted to Engineering Analysis, 1988.

Gray, L.J., Evaluation of Hypersingular Integrals in the Boundary Element Method, preprint, 1988.

Korobov, N.M., "The Approximate Calculation of Multiple Integrals Using Number Theoretic Methods," Dokl. Acad. Nauk. SSSR 115(1957):1062-1065.

Kvinge, T., M. Vestrheim, G. Wedvich, and P. Skegstad, Acoustic Remote Sensing Instruments for Monitoring of Polar Ice Drift, CMI Report 1988:51, 1988.

Petersen, J., and R. Renaut, Seismic Wave Propagation Using a Hypercube Multiprocessor, BSC Report 88/8, 1988.

Petersen, J., T.H. Olesen, and C. A. Addison, Dissection on the Hypercube, a Domain Decomposition Method, BSC Report 88/10.

Petersen, J., and J. Lindheim, Simulation of Larger Dimensions on the Intel iPSC Hypercube, BSC Report 88/11.

Reichel, L., Fast Solution Methods for Fredholm Integral Equations of the Second Kind, BSC Report 88/20.

Vestrheim, M., P. Lunde, and P. Meldahl, High-Resolution Shallow Seismic Surveying Using Parametric Acoustic Source Technology, CMI Report 1988:50, 1988.

National Physical Laboratory, Teddington, U.K.

by Richard Franke.

The National Physical Laboratory (NPL) is located just southwest of London in Teddington. The NPL is the national standards laboratory for the U.K. and is responsible to the Department of Trade and Industry. It consists of the Divisions of Electrical Science, Information Technology and Computing, Materials Applications, Mechanical and Optical Metrology, and Radiation Science and Acoustics.

My visit to the Division of Information Technology and Computing was arranged by J. G. Hayes. This division is involved in communications, mathematical software, software engineering, and advanced information processing. It is also responsible for the computing services for the laboratory. The Mathematical Software Group, which also conducts joint projects with other NPL divisions and external organizations, is concerned with mathematical research and numerical analysis, algorithms for metrology, and neural networks. My discussions were with those working in numerical analysis and metrology.

The NPL has a long history of involvement in the development of high-quality mathematical software (James H. Wilkinson, developer of backward error analysis and a heavy contributor in the development and analysis of algorithms for linear algebra and matrix eigenvalue problems spent his career at NPL). The NPL has been a major contributor to the Numerical Algorithms Group, Ltd. (NAG) library of mathematical software from its inception, and is still making contributions to it. The NAG also markets the NPL Data Approximation Subroutine Library (DASL), which contains extensive facilities for curve and surface fitting by polynomials, splines, and other functions. I will discuss some recent work and some work currently in progress at NPL.

Mathematical Software in Ada

The NPL has been involved with the programing language Ada for about 10 years, especially from the point of view of its use for numerical computation (see Cox and Hammarling, 1980). Ada does not include elementary mathematical functions as part of the language (unlike Fortran, for example). According to Dr. George Symm, this should be viewed as an opportunity for numerical analysts to "do it right" rather than having the compiler writers provide a convenient version of the elementary functions. In order to provide assistance in the implementation of portable libraries, NPL, together with the Centrum voor Wiskunde en Informatica (CWI) in Amsterdam, generated a set of practical guidelines for the use of those wanting to develop software in Ada (Symm, et al. [1984], and revised form, Ford, et al. [1986]). After this initial and necessary step, NPL and CWI--in collaboration with NAG and with assistance from the University of Liverpool and Trinity College Dublin (represented by the National Institute for Higher Education)--have been working to produce a pilot implementation of basic modules for large, portable numerical libraries in Ada. The core modules include

- The elementary functions
- Error mechanisms
- Quadrature
- Basic linear algebra
- Linear algebra
- Random numbers
- Ordinary differential equations
- Partial differential equations.

The work carried out so far at NPL is in the approximate solution of Laplace's equation with Robin bound-

ary conditions in two dimensions by the boundary element method and the least squares solution of overdetermined systems of linear equations, which is used by the former (see Symm, 1987). Current Ada software development work underway at NPL includes the use of the boundary element method for the solution of PDE's, and investigation of the use of Ada for parallel algorithms.

Metrology and Numerical Analysis

A typical problem in metrology is to determine from a set of measurements the amount by which a nominally round workpiece fails to be round. British standards define the deficiency in terms of the difference between the largest and smallest radii of the workpiece, measured from one of several possible centers (one of the possibilities is the center of the circle obtained by a least squares fit to the measured data). There are good and bad algorithms for computing the solution of this and similar problems in metrology, and NPL has a development program underway for a set of modular routines for their efficient and stable solution. Some recent references include Forbes (1987) and Cox and Jones (1988).

The problems in metrology often lead to overdetermined systems of linear equations with a few unknowns and many equations, perhaps within an iteration solving a nonlinear problem. Accordingly, NPL has been studying the use of parallel processors to solve such "tall, skinny" systems of equations. In a certain sense the problem is very well suited to parallel computations (at least with a moderate number of processors) since on a machine with p processors, QR decomposition can be applied independently to each of p (approximately equal sized) blocks of the matrix, with the very much smaller pairs of upper triangular blocks then being processed in the usual treelike fashion to the final QR decomposition. These problems are being investigated on a PC with a Transputer board with four processors. A 28-node (to be upgraded to 64 nodes) Computing Surface from Meiko is available at the laboratory.

The construction of calibration curves for immunoassay systems involves curve-fitting data under certain constraints upon the fitting function. For example, the curve may be required to have a nonnegative (or nonpositive) first derivative and nonnegative (or nonpositive) third derivative. Such a curve is called a *smooth sigmoid* curve. Because of the relative immunity of l_1 approximations to highly erroneous points, Cox and Jones (1988b) have used this measure of the error in a constrained quadratic spline approximation (for which the conditions are linear in the parameters of the spline) to immunoassay data. The B-spline basis is used, and for given knots and weights, the problem is formulated as a linear programing problem, and then solved using the Barrodale-Roberts algorithm (Barrodale and Roberts, 1980). The outer algorithm is iterative and determines the knot locations as well as the number of knots (up to a user-specified maximum), along with the weights for the data points.

Conclusion

The NPL has a long history of successful development of efficient and stable numerical algorithms for the solution of mathematical and scientific problems, and this continues to influence their work. It is often the case that these efforts are directly related to their internal work (such as the software for metrology), but this is not uniformly the case. The early NPL involvement in developing Ada programs for numerical computation is perhaps surprising, but certainly welcome. Their efforts to help define guidelines for such projects undoubtedly will have a long-lasting and beneficial effect.

References

Barrodale, I., and F.D.K. Roberts, "Algorithm 552. Solution of the Constrained l_1 Linear Approximation Problem", ACM Transactions on Mathematical Software 6(1980), 231-235.

Cox, M.G., and S.J. Hammarling, Evaluation of the Language Ada for Use in Numerical Computation, NPL Rpt DNACS 30/80, (July 1980).

Cox, M.G., and H.M. Jones, An Algorithm for Least-Squares Circle Fitting to Data with Specified Uncertainty Ellipses, NPL Rpt DITC 118/88, to appear in the IMA Journal of Numerical Analysis (June 1988).

Cox, M.G., and H.M. Jones, An Automatic Algorithm for Immunoassay Curve Calibration Using Controlled Quadratic Splines, NPL Rpt DITC 116/88, (April 1988b).

Forbes, A.B., Fitting a Circle to Radially Suppressed Data, NPL Rpt DITC 103/87, (December 1987).

Ford, B., J. Kok, and M.W. Rogers, eds., Scientific Ada, Cambridge University Press, Cambridge, 1986.

Symm, G.T., B.A. Wichmann, J. Kok, and D.T. Winter, Guidelines for the Design of Large Modular Scientific Libraries in Ada, NPL Rpt DITC 37/84, (March 1984).

Symm, G.T., Contributions to a Numerical Library in Ada, NPL Rpt DITC 98/87, (August 1987).

PHYSICS

The Physikalische Technische Bundanstalt, Braunschweig, West Germany

by Dean L. Mitchell. Dr. Mitchell is the Liaison Scientist for Solid State Physics in Europe and the Middle East for the Office of Naval Research European Office.

Introduction

The Physikalische Technische Bundanstalt (PTB), established a century ago, is a direct descendant of the Physikalische Technische Reichsanstalt (PTR) which was the first national research laboratory established for the purpose of conducting basic research in the physical sciences independent of requirements to satisfy educational or commercial goals.

The PTR was established by a Reichstag act in March 1887 and began operations later that year in temporary laboratories in the Berlin Charlottenburg district. The PTR was a forerunner for the National Physical Laboratory (NPL) established in 1900 in the U.K. and the National Bureau of Standards, now National Institute of Science and Technology (NIST), established in the U.S. in 1901.

From the beginning, the PTR was recognized as a research institution whose mission was to conduct basic research in the physical sciences and engineering. The scientific role of the laboratory was clearly evident in the composition of the first Kuratorium (Advisory Board) selected to provide scientific guidance for the PTR. The Kuratorium included Ernst Abbe, Rudolf Clausius, Hermann von Helmholtz (first president), Wilhelm Roentgen, and Werner Siemens.

The PTR's central theme was to make beneficial contributions to commerce and technology. Scientists at PTR gave priority to research investigations of the metrologies required to establish national and international standards of weight and measure. Also, they recognized the role of new techniques and instrumentation in the organizational separation in two departments--a physical department with laboratories for thermodynamics, electricity, and optics; and a technical department with laboratories for precision instruments, heat and pressure, electricity, and optics.

The PTR has a distinguished record of research accomplishments. Willy Wien, a student of von Helmholtz, developed the radiation law that now bears his name. He left the PTR in 1896 for an academic position, but later served on the Kuratorium from 1912-1928. Albert Einstein joined the PTR in April 1914 as a guest scientist and while there, established a collaboration with Johannes Wander de Haas; they discovered the gyromagnetic effect in metals--Einstein-de Haas effect. After his departure from the PTR, Einstein continued to serve on the Kuratorium until 1935.

A list of the scientists who were involved in research at the PTB in the first half of the 20th century reads like a who's-who in modern physics. This research topic list includes many of the major physics subfields that emerged during that period. Hans Geiger-the study of radioactivity; Max von Laue-the theory of x-ray diffraction; Walther Meissner-researches in superconductivity; Walther Nernst-pioneer in physical chemistry; Friedrich Paschen-studies in optical spectroscopy; Heinrich Ruben-research connecting the optical constants of metals with electrical conductivity, and Johannes Stark-research into the effects of electric fields on atomic spectra.

During the latter years of World War II, most PTR laboratories were evacuated from Berlin to current East Germany. In West Germany, physicists resumed research at Charlottenburg at the end of the war and made moves to establish a research institute to succeed the PTR. A panel, chaired by Max von Laue, was formed in 1947 to guide the establishment of a federal institute--the Physikalische Technische Anstalt (PTA)--on a redundant aircraft research establishment site in Braunschweig, West Germany. Wilhelm Kosters was the first president of the PTA.

The PTA was established by the West German government to serve as the state institute for physics and technology for the Federal Republic of Germany and presently is under the jurisdiction of the Federal Minister of Technology with a new name--the Physikalische Technische Bundanstalt (PTB). The PTB is responsible

for metrology and sectors of safety engineering, notably in mining and nuclear energy (waste management).

PTB Organization

Primary Research Components

- Mechanics and Acoustics-Rudolf Martin
- Electricity-Volkmar Kose
- Heat-Heinrich-Hans Kirchner
- Optics-Klaus Dorenwendt
- Precision Engineering-Horst Kunzmann
- Atomic Physics-Siegfried Wagner.

Secondary Research Components

- Reactor Radiation-operation of research reactor, metrology, and online data processing
- Technical and Scientific Services - fundamental physics, technical services, and data processing
- Berlin Institute-high and low temperature, physics, radiation physics, and BESSY beam lines
- Safety Engineering-mine and nuclear safety, and long-term nuclear waste.

Additionally, the PTB supports the German Calibration Service, with field offices distributed throughout Germany to provide calibration standards for commerce and technology.

In several PTB divisions, research is done in solid state and low temperature physics. Low temperature physics is centered at the Berlin Institute, Low Temperature Physics Laboratory, Hans-Dieter Hahlbohm, director. At the Berlin Institute, the low temperature research is done on cryogenic and measurement techniques and the physics of matter at cryogenic temperatures; i.e., liquid helium and superconductivity. Research on superconducting devices; i.e., Josephson junctions, is carried out at Braunschweig in the Electricity Division sector headed by Volkmar Kose. There has been notable success in developing uniform and stable arrays of 1440 Josephson junctions arranged in series as a prototype for a one-volt standard. The ultimate aim is to develop a voltage standard calibrated directly in terms of the primary time (frequency) standard. Leendert Bliek heads research on new superconducting materials of potential use in Josephson junctions and superconducting quantum interference devices (SQUIDS) carried out in the electrophysics sector.

Dr. Bliek is involved in research on the quantum Hall effect (QHE), discovered by Klaus von Klitzing, in Gallium-Aluminium-Arsenide (ALGAS) quantum well structures. The QHE devices are being investigated at the PTB for possible use as resistance standards that could be defined in terms of fundamental physical constants and thus would be independent of material parameters. In research carried out at the high field laboratory at Grenoble, von Klitzing observed that the Hall conductance for two-dimensional (2-D) electron systems, as in surface inversion layers or quantum well devices, was quantized in multiples of e^2/h This leads to resistances with quantized values of 25, 812/n Ohms, where n is an integer. To date, the precision of this qualification has been verified to about one part in 10^8.

Research at the PTB is directed toward determining the stability and precision of QHE devices and circuit elements required for a resistance standard, and to explore QHE device performance in terms of material and fabrication parameters. On the practical side, an ALGAS device fabricated by G. Weimann at the Research Institute for the German Post Office, has operated successfully for over one year while cooled continuously to liquid helium temperatures. Recently, the physics of QHE devices has been investigated in terms of dependences of the of Hall-plateau widths as a function of current density and as a function of irradiation levels. In the first study, the width of the Hall plateau for occupation of the second Landau sub-band was found to vary linearly with current density for narrow, one micron channels. Additional structure was observed in the breakdown region. This structure depends on width of the channel and was tentatively explained in terms of a model for quasi-elastic inter-Landau-level scattering (QUILLS) proposed by L. Eaves, Nottingham University, U.K. F.Y. Wees, Delft University, The Netherlands, observed similar structure in narrow channels. They ascribed the structure observed in their experiments to ballistic transport effects.

They investigated plateau width variation as a function of defects 6-meV-proton induced irradiation. The dependence was measured as a function of fluence following a 270-K anneal to eliminate transient effects. The width increased with fluence and moved to lower fields as expected with the localization model for the QHE. Futhermore, the width was found to scale with the parameter B/μ where B is the magnetic field and μ the mobility at $B = O$. Bliek developed arguments to relate this parameter with the density of localized states.

Bernard Kramer heads the PTB theory group located in the Technical and Scientific Services Division. Its title--Fundamental Physics--is misleading since the group's main research interests are in studies of disorder, localization, and stochastic effects in condensed matter systems. Recent work has focused on the following topics: the interpretation of the quantum Hall effect; investigation of the metal-insulator transition in disordered solids; localization of classic wave phenomena; and, stochastic processes with short range order.

The group's recent studies include the frequency dependence of the conductance of a linear disordered chain and the conductance of small scale systems in the ballistic regime. It is well established theoretically from the work of Landaur and others that the direct current (dc) resistance, conductance and their fluctuations for a one-

dimensional wire would increase exponentially with length and thus would not approach an average value in a statistical mechanical sense. Kramer and colleagues have calculated the frequency dependent conductance of a one-dimensional chain using a tight-binding Hamiltonian with diagonal disorder. For weak disorder, an oscillatory behavior was predicted as a function of frequency and of the sample length. In the asymptotic limit, the fluctuations decay less rapidly than the conductance thus the asymptotic average is not defined consistent with the known result for the dc case.

The theoretical investigations of the dc conductance for ballistic electrons in wires of constrained width reveal quantized steps as has been observed by van Wees, as mentioned earlier, Pepper at Cambridge University, U.K., and others. This quantization is shown to be independent of the length of the channel and can be tuned by variation of the width, the Fermi energy or the magnetic field while keeping the other two parameters fixed. Two new phenomena were predicted in the presence of weak disorder: anti-resonances were predicted between adjacent plateaus; and, the alternating current conductance was predicted to exhibit oscillatious because of the interference introduce via free electron states.

Report on Eleventh International Conference on Raman Spectroscopy (ICORS XI) London, September 5-9, 1988

by A.K. Ramdas. Professor A.K. Ramdas is from the Department of the Physics, Purdue University, West Lafayette, Indiana.

Introduction

The Eleventh International Conference on Raman spectroscopy (ICORS XI) was held in London, September 5-9, 1988, at the Institute of Education, University of London. The ICORS series, beginning with the first one in Ottawa in 1969 and the second one in 1970, is now organized biennially. The importance attached to these conferences is indicative of the impact Raman spectroscopy has had in physics, chemistry, materials science, and biology. Practitioners of this powerful spectroscopic tool find the ICORS very profitable to learn the latest in theory, experiment, and instrumentation, and appreciate advances in areas beyond that of their own specialties. The exhibits displayed by the manufacturers gave the participants a first-hand opportunity to learn all about such products as new spectrometers incorporating multichannel detection and Fourier-Transform-Raman.

The invention of the laser in 1960 and its application to Raman spectroscopy in 1962 have made inelastic light scattering a powerful scientific tool. With major innovations in techniques; e.g., photoelectric detection, holographic gratings, piezoelectrically scanned Fabry-Perot interferometers, tunable dye lasers, the scope of the field is now vastly extended. Extreme physical conditions--high magnetic fields, ultrahigh pressures--are experimentally tractable. Time-resolved Raman spectroscopy has profound applications for systems evolving with time scales as small as a Femto-second.

The Conference was structured with plenary lectures, poster sessions, and discussion sessions. The time allocated to plenary lectures and the selection of the topics and the speakers resulted in high quality, authoritative, indepth presentations. The poster sessions grouped efficiently according to common themes and the displays skillfully organized by the authors made them very effective. The discussion groups stimulated orderly but spontaneous discussions and commentary on many current topics. The Organizing Committee deserves congratulations on making the entire proceedings--1,034 pages--available right at the outset.

Condensed Matter

Merlin, University of Michigan, Ann Arbor, gave an overview of Raman Studies of Acoustics Phonons in Periodic and *Non-Periodic Semiconductor Superlattices.* The study of propagating and confined excitations--vibrational, magnetic, or electronic--in structures modulated on a submicron scale represents one of the most exciting areas in semiconductor physics. *Zone-folding* effects in the acoustical and optical phonon spectrum and *confinement* effects in the optical phonon spectrum and the special aspects of quasi-periodic (Fibonacci) lattices are some of the highlights covered in this lecture and a poster presentation. Surface Enhanced Raman Spectroscopy covered in a plenary lecture by Moskovits, University of Toronto, Canada, and in an entire poster

session testify to the intense activity in this extraordinary phenomenon. The phenomenon, though not yet fully explained theoretically (...the "electromagnetic theory seems to have been the most successful..."- Moskowvits) has been adopted by chemists, electro-chemistry surface physicists, and biologists. The plenary lecture by Guntherodt, Physikalisches Institut, Aachen, focused on intermediate-valence rare-earth compounds and heavy-fermion actinides. The review of Raman and Brillouin spectroscopy applied to this fascinating class of crystals highlights intriguing aspects such as charge and spin fluctuations (Guntherodt has been an active contributor to this field). Raman spectroscopy has been exploited with spectacular success in the study of materials at ultrahigh pressures, thanks to the Diamond Anvil Cell. Swanson, Los Alamos National Laboratory, New Mexico, gave a plenary lecture capturing the excitement of physics at pressures as high at 30 GPa. The poster sessions on Inorganic Materials and Matrices, The Solid State, Phase Transitions and Effects of Temperature and Pressure, Low Dimensional and Amorphous Solids, and Semiconductors and Superconductors dealt almost exclusively with topics in Condensed Matter.

A discussion session--*Solid State*--featured several condensed matter practitioners of Raman spectroscopy. The topics discussed were diverse, including a historical account of the role played by Raman spectroscopy both in the pre- and post-laser period (Ramdas). The intense activity in semiconductor physics (Cardona), microstructures of semiconductors (Tsang), superlattices (Lockwood), and incommensurate phases (Pick) were covered in short presentations followed by considerable audience participation.

A discussion session and Poster session focused on the *High T_c Superconductors* that burst upon the physics scene in late 1986, early 1987. Raman spectroscopy was immediately applied to these oxide superconductors and numerous studies have been published. The complexity of the crystal structure and the poor sample characterization in the early stages--polycrystalline, sintered nature, the lack of precise knowledge of oxygen concentration--led to conflicting results. A discussion group chaired by Burstein produced a vigorous debate that focused on the phonon spectra in the 30-40-K materials derived from La2CuO4 and the 90-95-K materials based on the quaternary Ba2YCu3O7 spin waves gap excitations. In single crystal YBa2Cu3O7-δ, evidence for gap excitations in the Raman spectrum has been reported (Cooper et al. Phys. Rev. B 37, 5920 [1988]). Lyons et al. (Phys. Rev. Lett. 60, 672 [1988]; Phys. Rev. B 37, 2353 [1988]) report observation of spin-pair excitations in Ba2YCu3O6+ ,0< <0.9, with an antiferromagnetic exchange energy of J=950cm-1. Implications of these observations for the correct microscopic theory, yet to be formulated, caused considerable excitement during the discussions.

STRUCTURAL DYNAMICS

Structural Dynamics Computational Models Group (Component of Group for Aeronautical Research and Technology in Europe - GARTEUR)

by David Feit. Dr. Feit is the Liaison Scientist for Acoustics and Mechanics in Europe and the Middle East for the Office of Naval Research European Office. He is on leave until January 1990 from the David Taylor Research Center, where he is a research scientist in the Ship Acoustics Department

Introduction

Using computers, the design of complex structures can now be accomplished using a computational model of the structure. These computational models should be able to accurately predict the dynamic response of the system. To establish the credibility and subsequent utility of these models, experiments on physical scale models or prototypes of these structures are often conducted in parallel and the results compared to the computational model results.

To analyze this comparison, sometimes it is useful to develop a computational model with fewer degrees of freedom than the full structural analysis computational model. This smaller model can be used to perform sensitivity analyses on parameters such as those caused by uncertainties in the precise geometry or boundary conditions of the original model. When experimental results

exist, it is necessary to integrate these with the computational model to improve or *update* the model. The best way to implement such procedures is currently being investigated at many institutions throughout the world. However, even without more definitive information, some commercially available computer codes already include such procedures in their routines.

With this as background, Action Group 11 (AG 11) of the Group for Aeronautical Research and Technology in Europe (GARTEUR) has been formed. This group generally addresses problems related to the "Refinement of Structural Dynamics Computational Models." Membership consists of individuals from Belgium the Federal Republic of Germany, France, the Netherlands, and the U.K., and are drawn from either academia, government research laboratories, or industry. Funds for individual efforts come from the institutions represented by those individuals. The chairman is Dr. R. Ohayon, French Office Nationale de Etudes et Recherches Aerospatiale (ONERA), and the vicechairman is Dr. D. Ewins, Imperial College of Science and Technology, London, U.K.

The group generally meets every six months, and I was invited as an observer to its last meeting held on December 6, 1988, at the ONERA facility, Chatillion, a near suburb of Paris, France.

AG II Objectives

The objective of the three-year research program is to develop and compare methods and computational tools that will allow the development of intermediate-size computational models that will mimic the more refined model of a proposed structural configuration. Then this simpler model can be more efficiently used for parameter changes or sensitivity analyses.

Emphasized Requirements:

- The ability to localize and quantify sensitive domains of the structure using numerically simulated experimental results with and without noise, and ability to determine the appropriate parameters of the revised model of lower order.
- The determined parameters are not unique but are to be determined through structural optimization algorithms (with or without constraints). This will relate the project to structural optimization problems.

Work Phase Outline

Phase 1. ONERA scientists have proposed a specific truss model upon which all participants will perform computations and analyses to establish their own methodologies. Independent results can be compared and differences rationalized in a collective effort.

Phase 2. ONERA scientists will provide numerically simulated *experimental* data for a modified structure in the form of a frequency response function calculated for a limited set of node points. The numerical data for this phase was generated for the truss model in which only changes in selected stiffness elements were introduced.

At this stage, each participant will also be developing individual updating methodologies. In subsequent stages, *experimental* data will be furnished by ONERA scientists for cases in which both stiffness and mass changes are introduced into the model calculations.

Phase 3. The participating scientists will apply the research tools and methods to a more realistic physical model as opposed to the simplified truss model. The ONERA group will also furnish to participants, data that will include noise. They will then perform the necessary calculations developed in the earlier phases.

Progress to Date

The group participants have met formally three times, at London during the 5th International Modal Analysis Conference (IMAC), April 1987; at Munich, April 1988; and at ONERA. Tenative dates of June 6 and 7, 1989, was set for the next meeting at the Royal Aerospace Establishment (RAE) in Farnborough, England, U.K. The results of this meeting will be discussed in a future issue of *ESNIB*. RAE's participant is Dr. Malcolm Nash.

At this stage, all participants have completed the calculations on the unmodified structure and have agreed about independently generated results. In addition, ONERA scientists provided the results of numerically generated data at 26 node points of the modified truss model with three degrees of freedom at each node. Results were provided for ten nodes and the structure modifications were known to be made only in the stiffness elements of the structure. The modifications, known only to ONERA scientists, were specified as localized to small areas of the structure. The participants have used their own methodologies to ascertain the modifications so they can update their finite element models.

Dr. Ohayon is finalizing a report on this first phase using the respective calculation results. Participants are reviewing and commenting on the report. Since I will continue to cover this project, I will publish comments on further progress. Project results will provide crucial information to the worldwide structural dynamics community in assessing the quality and reliability of computational dynamic analyses of complex structures.

SUPERCONDUCTIVITY

Superconductivity and Related Research at the University of Göttingen

by Alan F. Clark. Dr. Clark was the Liaison Scientist for Superconducting Materials and Electromagnetics in Europe and the Middle East for the Office of Naval Research European Office. He completed his tour at ONREUR and is now at the National Institute of Standards and Technology in Washington, DC.

Founded in 1737 by King Georg-August of Lower Saxony, the University of Göttingen now dominates the small town of Göttingen, West Germany as any large dynamic university would. Scattered in several departments is a wide variety of research on the new high temperature superconductors, but it is mostly focused in two of the nine institutes comprising the Physics Department--the Institutes for Low Temperature and Metal Physics.

Classical superconductivity research has been in progress in the Institute for Metal Physics for many years and, under the direction of Professor Dr. H.C. Freyhardt, has an excellent reputation, especially in the A15 compounds. Dr. Freyhardt also directs an informal coordination of the new high T_c superconductor research under a "HTSL" (hoch temperature superleitung) committee which holds monthly seminars and encourages extensive exchanges of information and specimens. For this work the university gets well over DM 10 million (about $5.6 million) this year, and it will more than double next year (don't forget salaries are paid in other ways). There was abundant evidence of extensive new equipmenteverywhere.

Research in the Institute of Metal Physics is focused in three areas--compound semiconductors, amorphous metals, and superconductors. (The productivity of this group's research and that from an associated crystal growth laboratory has spawned a new Institute of Functional Materials [see *ESNIB* 89-03:45-46 (1989)].) The Ge, CdTe, and GaAs are the semiconductors studied most extensively with large crystals being grown by modified Bridgeman techniques. The Ge is being grown as bicrystals with a nonelectrically active grain boundary for solar cell applications. The III-V compounds are being studied for the relation between structure and microstructure with carrier density and other physical properties. One unusual study involves tracking the diffusion of In by perturbed angular correlation with respect to Hall effect measurements.

Transition metal alloys, especially those of Nb, Zr, and Mo are being prepared in their amorphous state by melt-spinning. Of particular interest is the existence of short-range order and sometimes multiple phases as shown by X-ray, Mossbauer, and neutron scattering characterizations. For example, ZrFe, which is normally magnetic but when Zr rich is superconducting, shows a direct correlation of an increased critical temperature with increased short-range order. The metastable Nb alloys are also being studied to obtain the excess solubility as needed for an alternate route to the intermetallic superconductors.

The A15 superconductors, and particularly Nb_3Al, have been prepared via many methods in pursuit of a practical conductor of this highly desirable superconductor (high T_3 and high H_{c2}). The powder infiltration, laser annealing, plasma spraying, and modified "jelly-roll" methods have all been done. In addition, dual-gun sputtering of thin films with both parallel and multilayer approaches is used to study the fundamental structure both to compare with bulk materials and to initiate thin-film technology of Nb_3Al for eventual circuit applications. The secret to the success of the Nb-sintered-powder infiltration method is the use of an $Al_{88}Si_{11}$ eutectic for a low-temperature liquid infiltration and the addition of 1 percent Bi as an antiwetting agent. For an unknown cause, this method results in a high flux pinning force at high fields, a very desirable feature. The other more successful method is laser annealing of a Nb_3Al powder contained and compressed in a stainless steel tape. A rapid pass of a high-power laser yields rapid (5 msec) formation of the Nb_3Al without melting the stainless steel. Reasonably good (but not yet optimal) superconducting properties are obtained with a final anneal in a typical wind and react practical superconductor.

Other than the usual potpourri of high T_c superconductor preparation, structure, and other property studies germinated throughout the various research groups re-

sulting in varied results (and publications), two significant research efforts have shed some light on the new oxide superconductors. (A third effort to prepare and study thin films has just begun with a four-gun, dual-beam sputtering system about to be online and good laser-ablated YBCO films already prepared within a few weeks after receipt of an excimer laser.) The two productive efforts have both used combined expertise. Specific heat, resistivity, and Hall effect measurements have identified the charge carriers and their behavior with temperature in both single and polycrystals of YBCO, and Mossbauer studies of Fe substitutions have yielded information about the oxygen locations.

Dr. Winzel and colleagues of the Low Temperature Physics Institute have shown that the carrier behavior parallel to the c axis is not characteristic of semiconductors, as some have proposed, and definitely not like that which the Anderson RVB model predicts. In a surprising result, they have also shown by Hall effect measurements that the charge carriers within the grain boundaries or weak links are electrons and not holes, as within the grains.

Finally, in a study combining Mossbaur, X-ray, and neutron spectroscopy, Dr. Freyhardt's group has studied the addition of Fe to YBCO. Not only does the addition of the magnetic iron atoms not destroy the superconductivity, it draws in additional oxygen to the Cul sites and helps retain the superconductivity to above 15 percent Fe--well above an othorhombic to tetragonal transition. The addition of Ni up to 30 percent shows superconductivity, too, but a comparison of resistivity and susceptibility indicates only connectivity of a second phase. Fe addition to BSCCO is under study.

In conclusion, it should be apparent by now to perceptive readers that the group's strength lies in the careful application of many methods to obtain the necessary fundamental understanding before pursuing the development of a practical material. This strategy has already paid off and should continue to do so. Gottingen's Institute of Metal Physics is a group to watch.

TELECOMMUNICATIONS

The Deutsche Bundespost - Organization and Research

by J.F. Blackburn. Dr. Blackburn is the London representative of the Commerce Department for Industrial Assessment in Computer Science and Telecommunications.

Introduction

A change in the organization of the Federal Ministry of Posts and Telecommunications is expected in 1989. However, before the change can take place, the Parliament of the German Federal Republic must approve it.

At present, the Federal Ministry of Posts and Telecommunications has four main operating divisions--Postal Services, Postal Banking Services, and two divisions concerned with telecommunication. The Postal Services division is divided into three groups: (1) Organization, Personnel and Economic Management; (2) Postal Services and Engineering; and (3) International Postal Affairs and Postal Services and Chairman of the Executive Council of the UPU. The Postal Banking Services deals with Postal Banking and Money Services, Pensions Payment Service and Information Processing in Posts.

The first of the Telecommunications divisions has four groups: (1) Organization, Personnel Matters, Economic Management, Information Processing in Telecommunications and Logistics; (2) Broadcasting and Broadband Distribution Services; (3) Telecommunications Networks, Satellites, and Research; and (4) Mobile Radio and International Telecommunications Affairs.

The second of the Telecommunications divisions is also composed of four groups: (1) Telephone Service/Network, Integrated Services Digital Network (ISDN), and Surface Construction; (2) Terminal Equipment and Marketing; (3) Regulations of Use, Telecommunications Rights and Laws, and Accounting Service; and (4) Text, Facsimile, and Data Services/Networks.

In addition to the above four divisions, there are five departments responsible for (1) Personnel; (2) Finances; (3) Central Organization, Building Construction, and Real Property; (4) Publicity and Market; and (5) Department for Central Matters.

Planned Organization Change

The German government appointed a committee, chaired by Professor Dr. Eberhard Witte, to recommend Bundespost organization. The organizational change planned for year end 1989 will follow closely the recommendations of Professor Dr. Eberhard Witte's commit-

tee reported in my summary of World Telecommunications '87 dated December 7, 1987.

The plan is to have three companies, wholly government owned but operating like private companies with profit/loss responsibility and ability to borrow money on financial markets. There will be a Postal Services Company, a Postal Banking Services Company, and a Telecommunications Company called Telekom which will comprise the two telecommunications divisions.

Competition is now allowed in customer premises equipment such as terminals and telephones. However, the state-owned company, Telekom, will continue to exercise a monopoly over the telecommunications network. This will be on condition that private service companies will be assigned leased transmission lines on appropriate and competitive terms. If this is not the case after a 3-year trial period, then the network should also be open to general competition.

The telephone service as the pure transmission of the spoken language will remain a state monopoly, but not the combined services with text, picture, or data which include the spoken language as well. In consequence, the further reduction of the state monopoly will come with the introduction of new telecommunications services which also include the spoken word.

The entry of private competitors into the terminals and value added services market means that Telekom will require freedom for entrepreneurial action.

The legislative, administrative, and regulatory tasks will remain with the Federal Ministry of Post and Telecommunications. Telekom, headed by a management oriented Board of Directors, will be responsible for the organization, use, and operational functions. This raises no constitutional problems in the Federal Republic. Subsidizing the postal services from the profits drawn from the telecommunications sector will be gradually discontinued. Effective with the new organization, the figures will be clearly shown on the Ministry's budget.

Research at the Deutsch Bundespost

The Direction of the Research Institute (Institute) of the Deutsche Bundespost (Bundespost) Telecommunication Engineering Centre does not intend to develop products by its own research. Rather, the technical knowledge based on in-house research is needed to be able to assess the products offered by manufacturers. The Institute must also be able to give technical guidance as to the direction in which products should be developed on the basis of technical findings. It is also necessary to participate in decisions at the European and international levels that are favorable to German customers; therefore, it is necessary to have the appropriate knowledge to be able to make the best choice.

The Institute's main branch is in Darmstadt and a smaller unit is in Berlin. There are 290 staff members in Darmstadt and 60 in Berlin, 130 of whom are scientists. About DM 30 million are spent each year on research contracts and equipment. The organizational scheme of the Institute is shown in Figure 1.

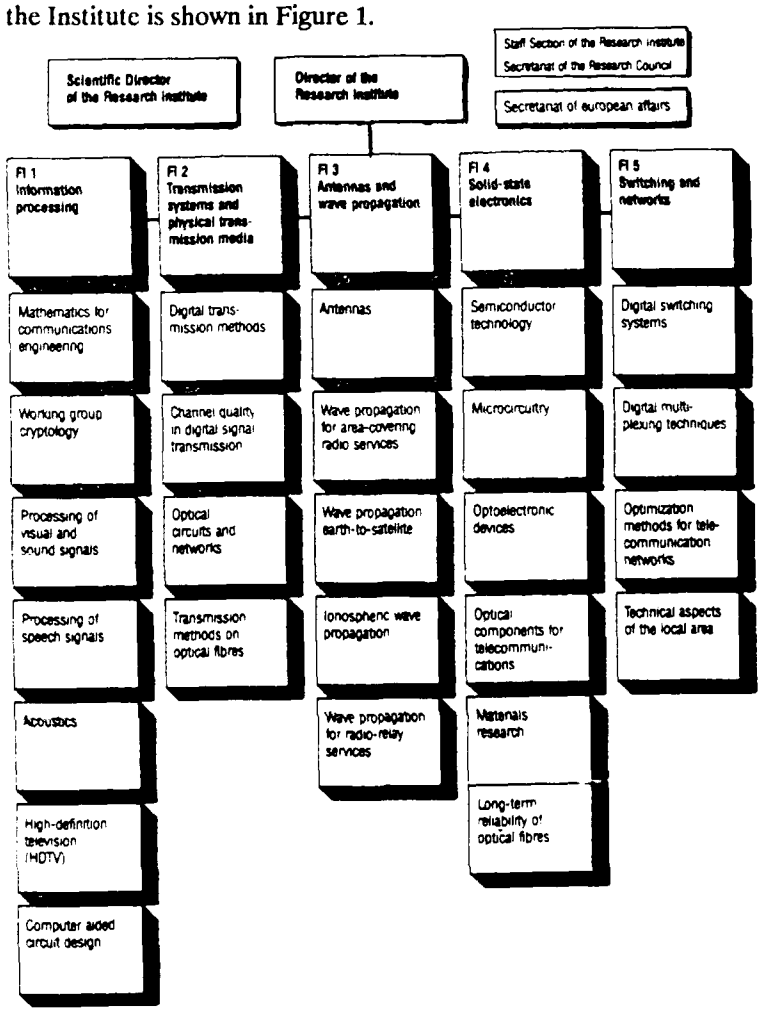


Figure 1. Organization Scheme of the Research Institute.

Work in each category outlined in Figure 1 is briefly described in the following paragraphs.

Information Processing

Digital representation on signals provides ideal prerequisites for the preprocessing of speech and image signals. The signals can be processed so that

- Redundant signal elements can be suppressed in the transmitter and reconstructed in the receiver without any loss of information
- Signal elements that cannot be perceived by our sensory organs spatially or temporally are suppressed
- Secure clear authentication or protection against unauthorized access

- Guarantee interference-free transmission in transmission channels subject to a large amount of interference; e.g., mobile communications.

Digital information processing allows logic operations between significant information units. Therefore, its methods form the basis to create the technical prerequisites for many new or improved communication services.

At present, work is going on to realize a videophone with improved image and sound quality for the 64kbit/s ISDN. With this device, it will be possible to transmit moving color pictures for individual communication on the existing copper wires of the present telephone network available in the whole country at low cost. For high-definition television (HDTV), a procedure compatible with the 625-line standard is developed that will make it possible to reduce the transmission capacity requirements by 50 percent without a visible degradation in quality. Thus, only two TV channels of the old standard will be necessary to transmit the HDTV signal of a resolution increased fourfold.

Because of the increased use of computers in the operational facilities of the Bundespost, man/machine communication on the basis of natural speech becomes ever more important. The researchers at the Institute conceive interactive systems making it possible to recognize the users' request independently of the speaker and with a low error rate. The audio response unit for unlimited vocabulary used is the text-to-speech synthesis system SAMT (text-to-text synthesis) developed in the Institute. The real-time implementation of very complex algorithms as they are developed in information processing today require many active circuits. Therefore, the Institute has its own laboratory to design large-scale integrated circuits.

Transmission Methods and Physical Transmission Media

In this field of research, the Institute concentrates on development of digital transmission methods for various transmission media ranging from the symmetrical star-quad twisted pair to the dispersion-shifted monomode fiber. Security measures against unauthorized access and misuse are gaining significance apart from aspects of reliability and profitability with the features being predetermined.

In addition to source coding measures not carried out in this field of research, digital transmission methods in any case require appropriate channel coding techniques that adapt the digitized source signals to be transmitted to the characteristics of the transmission path. For this, it is necessary to determine the characteristics of the transmission paths by measurements, and to find out by computer-aided evaluation whether and how often multiple errors of a certain length occur in error bursts. Since the measuring instruments required are not available on the market, suitable measurement procedures must be developed and measuring equipment built within the Institute.

The mobile radio channel has particularly poor transmission characteristics, and attempts are made to get its variability as a function of time under control in channel coding by special error protection procedure and detection methods with a memory facility.

In optical transmission, attempts are made to make optimum use of incoherent transmission methods by threshold decision as far as the characteristics of the components and fibers available permit it. The relevant components in the optical frequency range include lasers, repeaters and detectors, and frequency selective and non-frequency-selective passive branching equipment. This section of the Institute depends on contributions that partly come from the field of research *solid-state electronics* or from external institutions. On the other hand, the activities to implement the laboratory model of a transmission system on the basis of the heterodyne principle at 200 terahertz, which corresponds to a wavelength in a vacuum of 1.5 micrometers, are speeded up in the field of coherent optical transmission methods. After a test phase, this laboratory model will be tested in experimental networks of the Bundespost on existing fiber optic links under normal operating conditions.

Antennas and Wave Propagation

The objectives of the research in this field are to gather the scientific and technical knowledge required by the Bundespost to provide powerful and future-oriented radio systems.

Antennas with increasingly stringent performance characteristics such as gain, side-lobe level, polarization purity, adapted coverage of given service areas, and adaptive fading reduction, must be developed. The prerequisite for their availability is the timely development of application-specific hardware concepts, suitable software to model and optimize their properties, as well as of accurate antenna measurement techniques to examine and verify the hardware performance.

The transmission characteristics in radio communications are influenced by the atmosphere, the Earth's surface, by relative movements of transmit and receive antenna and matter in the radio path. Additionally, they are subject to time variation. Also, mutual interference occurs when radio networks become increasingly meshed. The purpose of research on wave propagation is to determine the effects of these phenomena experimentally and to develop models for radio systems design.

In the field of area-covering radio services, research is concentrated on developing network planning proce-

dures by a topographical database; hardware simulation of the radio channel to assist in system development; and the description of its most important figures of merit by measurements in terrains different in shape, extent of built up, and vegetation. The results of this work have recently been taken into account in the establishment of the radio telephone network C, in the planning of VHF transmitters for sound and TV broadcasting, and in the specification of the new pan European digital mobile telephone network D.

Wave propagation in satellite communications is mainly impaired by precipitation in the frequency range above 10 GHz which leads to additional attenuation and a change of the polarization state. For the planning of operational satellites in the 20, 30 GHz range, a test program is being prepared in international cooperation that will make it possible to carry out propagation experiments with the OLYMPUS satellite from 1989 onward. Also, the scattering of radio waves caused by precipitation is being investigated. This scattering can lead to unintentional interference with other radio services. A measuring network consisting of several transmitters and receivers is used to record the intensity of scatter signals at different altitudes.

The formation of layers with different reflective indices in the near to ground atmosphere can lead to multipath propagation on terrestrial radio path and cause frequency selective fading that impairs digital transmission schemes. Apart from the statistical evaluation of the fading process parameters, the study of appropriate adaptive countermeasures is a subject of research in this field. Computer simulation has proved to be useful for this purpose. It allows the performance prediction of transmission systems before their hardware implementation.

As a service, short- and long-term forecasts of the propagation conditions in the high frequency range are issued for many users on the basis of observations. Software especially developed for this purpose makes it possible to carry out system studies from existing and planned shortwave radio communications. The average variation of the forecasts is less than 10 dB.

Solid State Electronics

The III V compound semiconductors such as indium phosphide (InP), gallium arsenide (GaAs), and indium gallium arsenide phosphate (InGaAsP) play an important role in optical broadband communication. Joining different thin single-crystal layers by crystal growth techniques and epitaxial processes produces heterostructures whose optical and electrical properties are used in devices for light emission, light detection, and fast signal processing. The research subjects dealt with in solid state electronics include semiconductor devices, microcircuitry, and optical devices for information transmission. Also, materials research supports and complements device technology with analytical methods.

One of the most recent results is in InGaAsP distributed feed-back laser (DFB) with a mushroom-shaped structure developed in the Institute laboratory. It emits a nearly monochromatic light of a wavelength of 1.5 micrometer, which is subject to minimum attenuation in the optical fiber used for transmission and can be modulated very fast. In a transmission experiment, a 60-km monomode fiber link was achieved without repeaters with such a DFB laser at a modulation rate of 2.23 Gbit/s (bit error rate less than 10(-9). For light detection an InGaAs/InP PIN photodiode also developed at the Institute was used.

To handle the high bit rates required for the transmission experiment, digital circuits in hybrid technology were developed using the fastest available GaAs integrated circuits on the market. The change to silicon integrated circuits in bipolar technology as active devices in integrated hybrid circuits made it possible to double the bit rate to 4.45 Gbit/s. Research on high speed devices for implementation in integrated circuits also belongs to the research tasks like the systematic research into the quartz fiber for its physical properties and the long-term reliability of optical cables.

Switching and Networks

The Institute's activities in this field include network architecture, network components, and network planning procedures. The objective is to support the Bundespost in providing a broadband ISDN for interactive and distributive/retrieval services. In addition to the services available in the narrowband ISDN, new services are planned such as high quality visual communication, retrieval of films or images in interactive dialogue, and broadcasting services. The possible use of new switching principles and multiplexing procedures is being examined and the performance of such networks must be determined. The Institute is testing a new transfer mode that gives great flexibility to these networks, called Asynchronous Transfer Mode (ATM). With this technique, the network transports user information in cells of fixed size consisting of a user information field and a header. Connections are identified by information contained in the headers associated with them. The necessary multiplexers, synchronization procedures, and exchanges using selfrouting switching networks are being investigated.

The Institute studies the suitability of optical techniques for broadband circuit switching, as well as possible applications of optical switching.

Also, the components for distribution services are investigated. The studies concentrate on distribution

switching networks with rearrangement of existing connections and multiplexers for high quality image and sound signals transmission.

For network planning, the Institute develops procedures for network analysis and synthesis. Studies are being carried out to optimize transmission networks at minimum cost. Great importance is attached to reliability and trunk group dimensioning in integrated services networks. Strategies are underway for capacity allocation in transmission networks and on trunk groups.

The Institute is treating questions relating to the structure of the subscriber access network. Another field of activity is the user network interface.

The Institute also deals with techniques for the formal description of the functional behavior of systems and interfaces to make these systems suitable for tool support treatment.

Comments

The planned reorganization of the telecommunications service in Germany, which will likely be effective January 1990, will be very similar to that which was effective January 1989, in the Netherlands--a company performing in many ways like a private company yet wholly owned by the government.

In-house research of the German telecommunications organization is relatively small compared to some other smaller countries. The reason for this is that the Bundespost depends on companies for product development. Their research is to enable their assessment of products offered and to better determine what is possible to support their service.

NEWS, NOTES, AND ABSTRACTS

Change of Command at ONREUR

In May 1989, CAPT Terry J. McCloskey completed his tour as ONREUR Commanding Officer and was relieved temporarily by CDR John Simpson.

On July 5, CAPT Victor L. Pesce became Commanding Officer of ONREUR. Before assuming the ONREUR command, CAPT Pesce had served as OIC OPTEVFORDET Sunnyvale, California, since 1987, directing operational testing of command, control, communications, and intelligence systems supporting afloat battle commanders.

Change of Editors at ONREUR

Mr. C. J. Fox, who served as ONREUR's Editor for more than three years, returned to Naval Underwater Systems Center New London, Connecticut. Mr. Fox will retire soon and will live in both Connecticut and northern California.

Ms. Connie R. Orendorf is now ONREUR's Editor. Before moving to London, Ms. Orendorf was the Editor of the Navy Domestic Technology Transfer Fact Sheet located at Naval Surface Warfare Center, Dahlgren, Virginia.

Other Staff Changes at ONREUR

Mr. Robert Ryan is serving as a Liaison Scientist on the staff of ONREUR. In this position, he reports on selected areas of mathematics and computer science. He is on leave from Office of Naval Research, Arlington, Virginia, where he is the Director of the Special Programs Office.

Dr. Michael J. Koczak, a materials engineer on sabbatical leave from Drexel University, Philadelphia, Pennsylvania, is serving as a Liaison Scientist in materials engineering at ONREUR.

Dr. Claire E. Zomzely-Neurath, Liaison Scientist for Biochemistry, Neurosciences, and Molecular Biology in Europe and the Middle East, left London having served for five years at ONREUR. Dr. Neurath is relocating to San Diego, California.

Noise Reduction of Machinery Installations Course

On October 23-27, 1989, a course entitled "Noise Reduction of Machinery Installations by Vibration Isolation" will be offered at Noordwijkerhout, the Netherlands. This course will provide engineers with the latest information from applied research and will improve their knowledge and understanding of structureborne sound isolation. The knowledge has many practical applications to a wide range of industrial products, including aircraft, motor vehicles, railway vehicles, processing plants, buildings, and consumer products.

The course has been prepared by a group from European organizations supported by the European Community action program for Education and Training for Education and Technology (COMETT). Course instructors have been recruited from TNO Institute of Applied Physics (TPD), Delft, the Netherlands, the University of Southampton Institute of Sound and Vibration Research

(ISVR), U.K., and Metravib RDS, Lyon, France.

Over a 4-day period, the instructors, all internationally known experts, will present the course with lectures, case histories, and laboratory demonstrations. The demonstrations will take place at the TPD laboratories in Delft.

The course lecturers are:

- Ir. J.G. van Bakel, head of the Research Section of the Ship Acoustics Department TPD
- Dr. B.J. Dobson, Senior consultant in the ISVR, University of Southampton
- Ir. B. Garnier, head of the Vibration Group at Metravib
- Prof. J.W. Verheij, Senior scientist and part-time professor at Eindhoven University
- Prof. R.G. White, Director of ISVR and Professor of Vibration Studies
- Dr. T. ten Wolde, head of the TPD Acoustics Division

The enrollment fee is 1500 ECU/Dfl 3515 and includes lecture notes, meals and refreshments, accommodation, and taxes. Enrollment deadline is September 22, 1989, and enrollment is limited. For further information, contact:

TNO Institute of Applied Physics
Administrator, Course COMETT
PO Box 155
2600 AD Delft
the Netherlands

Dr. David Feit

Dutch Marine Information Service

Marine Information Service (MARIS), is a referral service for improvement of information and data provision in relation to the North Sea. The Netherlands government supports and operates MARIS in cooperation with departments, research institutes, and industry. MARIS operates a public, online information service, giving a guide to marine knowledge, information, and measurement data available in the Netherlands.

MARIS is brought online in cooperation with a professional host center. The first steps involve a database with references to available measurements or samples and resulting data products, and a database for industries and their specific services, disciplines, and products ("Yellow Pages").

The pilot phase began in March 1989, and beginning in September 1989, MARIS will offer online search capabilities, all menu-driven in English. MARIS is working on a directory of oceanographic instrumentation, and much more is to follow.

A MARIS customer desk will be available to provide assistance and advice. A foundation--Marine Information Service--will take care of exploiting and further developing the system, and the organization will act as the National Oceanographic Data Center.

Paul Geerders of the Netherlands Center for Oceanographic Data (NCOG) is now working as a consultant, and will keep his personal mailbox P. GEERDERS. However, the organization he represented for ten years, no longer exists. MARIS will be responsible, in close collaboration with the Netherlands Marine Research Foundation (SOZ), for most of the services NCOG provided.

Dr. Dean Mitchell

European Initiative: Pulsed Field Magnets

Five high magnetic field facilities have formed a consortium with the support of the Council of Ministers for the European Community (EC) to develop techniques and hardware for building pulsed magnets with peak fields in excess of 50T. The participants include; The Natuurkundig Laboratorium of the University of Amsterdam (Paul Frings and Willem Mattens); the High Field Magnet Laboratory at Grenobie (Peter Wyder and Hans-Jorg Schneider-Muntau); the Service National des Champs Intense at Toulouse (Solomon Askenazy); the Laboratorium voor Lage Temperaturen en Hoge-Velden Fysika at Leuven (Fritz Herlach); and, the high field laboratory at Oxford University (David Dew-Hughes and Harry Jones). During the first phase, the funds provided by the EC will be for projects to develop improved conductors for pulsed magnets. The funding for this phase has been set at a level of 700K ECUs over 3 years beginning approximately 1 April 1989.

Several conductor options are being explored including stainless steel jacketed copper wire, an Oxford specialty, filamentary Cu:Nb composites, as developed by supercon in the US and Ahlstom in France, and other similar composites. New pulsed-field magnet facilities are planned for Grenoble and Oxford. The quasi-static facilities at Amsterdam and Toulouse have approval for projects to develop 60T magnets with pulse times on the order of one second. The high field laboratory at Leuven has a versatile storage bank for coil testing and has an in-house program for coil development. To date, coils wound with Supercon wire have been operated successfully at Leuven to 50-55 T with 1-10 millisecond pulsed times. Some annealing was required to relieve the brittleness of the wire, as received. Toulouse has reportedly operated a large coil successfully at 60T without major deformation or damage.

The participants in the EC consortium meet fairly regularly to report on progress and to exchange information. There appears to be little interest in pooling multi-national resources in a single large central facility, but rather the concensus appears to be to develop smaller regional facilities adapted to local use. A significant development is the

rather strong interest in the European solid state and condensed matter physics communities in the use of pulsed-field facilities with peak fields in excess of those provided by dc magnets. In the past, experimentalists were reluctant to dedicate major effort in developing the techniques and instrumentation required for pulsed field research. This attitude appears to be changing.

Dr. Dean Mitchell

ONREUR REPORTS AND MAS BULLETINS

Reports

To request reports, indicate the report number (in parenthesis after the title and author's name) on the self-addressed mailer and return it to ONREUR.

Computer Science

BRITE-EURAM 1989, by J.F. Blackburn. **(9-9-C)** The second Basic Research in Industrial Technologies for Europe-Europe/America (BRITE-EURAM) conference was held in Brussels, Belgium, in winter 1989. The primary objective of the program is to make European manufacturing industries more competetive in world markets.

BRITE-EURAM builds on earlier work of the BRITE and EURAM programs that already support 300 projects. For 1985-88, BRITE had European Community (EC) funds of 185 million ECUs and supported 215 projects. For 1986-89, EURAM has 30 million ECUs and supports 84 projects. The four major technical areas are (1) advanced materials technologies, (2) design methodology and assurance for produces and processes, (3) applications of manufacturing technology, and (4) technologies for manufacturing processes, each with several subareas.

In the opening address, Mr. Pandolfi, Vice President, The European Commission (Commission), stated that many BRITE participants have recently reported that they expect to realize commercial benefits from their projects within 5 years. Pandolfi urged that a strong set of links be created between different frameworks for European cooperation so ensure that EC R&D resources are used effectly.

In this report, Dr. Blackburn briefly reviews the following topics:

- The relevance of European community R&D program for industrial development
- Setting R&D priorities for an industrial company
- Customers, suppliers, and researchers: The opportunities and pitfalls in Europe for R&D collaboration
- Introduction of stability and plasticity phenomena into a computer-aided design project for metallic structures
- Predictive techniques for the analysis and design of fiber reinforced composite materials and structures capable of withstanding impulsive loading
- Development of standardized material transport devices for the sequential automation of the processing of flexible materials
- Two- and three-dimensional garment modeling
- Sensor technologies for machine control and condition monitoring
- Optical sensors and fiber optic wavelength division multiplexing for process control
- Adaptive control of laser processing
- Links between R&D and standardization
- Brief review of materials development and application
- Brief review of product assurance technologies
- Brief review of applications of manufacturing systems.

The Commercial Opportunities for New Advanced Electronic Materials, by J.F. Blackburn. **(9-10-C)** The British government is committed to collaboration in R&D, both at the national and European levels. Most research is now directed toward materials to be used in VLSI, and toward techniques for producing these chips and packaging methods.

Most of the papers dealt with materials at the chip level which is dominated by large-scale integration. Papers were presented on the following subjects:

- Advanced electronic material
- Government policy and support for advanced electronic materials Silicon VLSI technology
- Status of gallium arsenide technology
- Specialty chemicals and materials for electronics
- Optical recording technology and materials requirements
- Commercial exploitation of advanced electronic materials
- Commercial opportunities for optoelectronics based materials
- Infrared and optoelectronic materials and their applications: a MOD perspective
- Advanced materials for electronic displays
- Likely impact of the high temperature superconductors

- Amorphous semiconductor electronics into the 21st century

International Open Systems Conference, by J.F. Blackburn. **(9-11-C)** On March 21 and 22, 1989, at the International Open Systems Conference, London, U.K., papers were given on Open Systems Interconnection (OSI) Perspectives, International Aspects of OSI, Conformance Testing and Certification, Standard Issues,and Migration Strategies.

OSI Perspectives. Despite its original direction, the system view has been obscurred. The following areas are important to establish the system context: (1) lower layers of the OSI Reference Model-Provision of the transport service, (2) application layer standard, (3) system building, and (4) major issues for a system approach.

International Aspects of OSI. Merging of telecommunications and computers leads to need for common standards in architecture and protocols in communication, and in operating systems and computer languages in computing.

Conformance Testing and Certifications. The conformance testing goal is to provide a base of discipline to the implementors and confidence to customers investing in OSI. The basic goal of the Conformance Testing Service (begun by the European Commission in 1985 to promote information technology and telecommunications standards) is to enable conformance of information technology products to standards based on the principles of independence, mutual recognition, and standardization.

Standard Issues. Identified systems management functions are for object management, state management, relationship management, error reporting and information retrieval, management service control, confidence and agnostic testing, log control, software management, and security management. NATO has selected a subset of ISO security architecture options.

Migration Strategies. According to Mr. Paul Frost, OSI Manager, Employment Department, Training Agency, tactics are to introduce a corporate network and a corporate approach to the need for communications, to introduce services giving a substantial fast payback, to introduce services that reduce reliance on specific suppliers, and to identify services that are required to meet business objectives.

MAS Bulletins

The following Military Applications Summary (MAS) Bulletins were published between 10 April and 21 July 1989. The MAS Bulletin is an account of accomplishments in European naval research, development, and evaluation. Request copies of the Bulletins, by number, from ONREUR.

25-89 Jet Float

26-89 Stoneguard 2000 Erosion Resistant Film

27-89 Stereoscopic Vision System

28-89 PILOT – A Radar For Cover Operations

29-89 ASSETS – ASsessment System for European Technology and Science

30-89 DM 109 Underwater Acoustic Signal

31-89 HYDROBALL – An Expendable Current Profiling System

32-89 BSAP Fender System

33-89 Portable, Pneumatic Machining Units

34-89 Space Highlights - 1989 Paris Air Show

35-89 European Hypersonic Technology Programs Update

36-89 French Spaceplane - HERMES Update

37-89 Antisubmarine Warfare Area System

38-89 Second Generation Night Observatopm Device

39-89 Twin 30 Compact Naval Mount

40-89 GY-90 Fiber Optic Gyro

41-89 Rescue Stretcher

Reports on European Science and Technology from Other Commands

Reports

Information on each of the reports listed below was furnished by the the following activity. Requests for copies of or information about the document should be addressed to:

EOARD - European Office of Aerospace Research and Development, Box 14, FPO New York 09510

Acoustics

Workshop on Analysis, Design, and Testing of Structures Subject to Thermal and Acoustical Loads, by LTC James G.R. Hansen, EOARD. (9 pp) [EOARD-LR-89-025]

This workshop was conducted 14-15 July 1988 in Southampton, England. Acoustic fatigue of hypersonic vehicles was a major discussion topic.

This report contains the program, a list of delegates, and a summary of the conclusions and recommendations from the workshop.

Aeronautics

Aerodynamic and Flight Control Research at University of Glasgow, by MAJ Tom Speer and LTC Fred Gilliam, EOARD. (6 pp) [EOARD-89-028]

The Aerospace Engineering Department at the University of Glasgow pursues a broad research program aimed at solving the problems of today. The research is concentrated in five areas: unsteady aerodynamics, hypersonic computational fluid dynamics, airfoil design methods, parameter estimation of helicopter aerodynamic and flight mechanics models from flight test data, and digital control systems using architectures with a high degree of parallel processing. This report describes the recent activities and accomplishments in aerospace research at Glasgow.

University of Strathclyde Industrial Control Unit, by MAJ Tom Speer, EOARD. (4 pp) [EOARD-LR-89-033]

The Industrial Control Unit (Unit), University of Strathclyde, Glasgow, Scotland, is the largest self funded unit in the U.K. universities. Directed by Prof. Michael Grimble and Dr. Michael Johnson, the Unit does both theoretical work in multivariable digital control and develops control systems for a variety of industries. The H-infinity control design techniques are highly developed, and the these are used to produce robust, self-tuning, adaptive controllers. Future directions for the Unit include the creation of a group dedicated to aerospace applications, and work in dynamic matrix control methods.

Electronics-Related Research in Italy, MAJ Parris Neal, EOARD. (4 pp) [EOARD-LR-89-036]

This report outlines some of the technical capabilities within several Italian industrial organizations. Elettronica S.p.a. is the major supplier of EW systems to the Italian Government, with strong research abilities in microwave components, especially TWT design and manufacture. Selenia is a large electronics group with products in search and control radars, communications, and integrated control systems. Much work is occurring in display systems design for the integration of map and other tactical data in a real time battle control system. Contraves Italiana S.p.a. also has considerable expertise in radar technology. Products include integrated radar and optical tracking weapons control systems. Also, much work is being done with 95 MHz and 3d antenna designs. Telettra Telecomunicazioni is an international communications company. Work is mainly in telephone communications equipment but some products include military communications equipment with ECCM protection. Research is centered around fibre-optic based systems and in-house development and production of high-power GaAs discrete semiconductors and analog integrated circuits. Their products include a 4-watt, X-band GaAs Fet with .5 micron, bridged gate structure. Olivetti is a major international computer manufacturer. Besides research into computer systems, it is working on text-to-speech and voice recognition systems.

Biotechnology

Biotechnology in Dublin, by MAJ Jim McDougal, EOARD. (5 pp) [EOARD-LR-89-023]

Ireland has a great interest in attracting modern clean industries and the development of a biotechnology industry is high on the list. They have set the stage by providing a framework for government/industry/university cooperation. In Dublin alone, three centers of excellence in biotechnology have been established. This report describes programs at University College, Trinity College, and the National Institute for Higher Education.

Chemistry

Chemistry Research Interests at University of South Hampton, by LTC Chet Dymek, EOARD. (20 pp) [EOARD-LR-89-017]

Several research programs at this top-ranked university have clear ties with Air Force research interests. Surface chemistry is focused on ultra high vacuum systems in which molecular and atomic beams impinge on very clean surfaces and scattered products are monitored. Ellipsometry and very impressive molecular dynamic calculations on surface films are other featured areas. Excellent work in the area of enzyme activity and molecular recognition has potential application to future development of biodegradation or synthesis of nitro-compounds. A unique method for studying metal oxide ions of interest in the upper atmosphere is also described. Finally, an invitation was extended to have FT-Raman spectroscopy done on samples from our laboratories using a prototype spectrometer developed at Southampton.

AFOSR Chemistry Research Interests at Trinity College, Cublin, by LTC Chet Dymek, EOARD. (7 pp) [EOARD-LR-89-029]

Chemistry at Trinity College tends to be strongly linked to applications, but the facilities, talent, and desire are there for excellent basic research to be conducted. The highlights for potential Air Force interests were in the areas of diffusion of species through polymeric solutions, the chemistry underlying electrochemical simulation of pitting of alloys and the development of a model relating surface pitting of turbine blades to fracture mechanisms, semiempirical molecular orbital calculations with an emphasis on accounting for and studying solvent effects, synthesis of enzyme-like catalysts for reactions involving nitro compounds, and studies of nonlinear optical properties of materials based on the "quantum dot" effect.

Optical Fibre Research at the University of South Hampton, by MAJ Parris Neal, EOARD. (12 pp) [EOARD-LR-89-018]

The University of Southampton, U.K. has one of the oldest fibre optic research groups in the world. The group was responsible for the invention of the Modified Chemical Vapor Deposition (MCVD) process of creating the bulk material for drawing a silica clad fibre. In the early 1980s, the research team turned to special fibres and has developed several novel fibres. The most well known is the "Bow Tie" polarization preserving fibre and the circularly birefringent fibre using a spun version of the bow tie fibre. Additionally, the group has been responsible for the creation of several "rare earth" doped fibres and is developing fibre based devices such as fibre lasers, distributed temperature sensors, current sensors, in-line optical amplifiers, and passive and active planar optical circuits for interconnecting VLSI circuits.

AFOSR Research Interests at the University of Limerick, by LTC Chet Dymek, EOARD. (14 pp) [EOARD-LR-89-0030]

Formerly the National Institute of Higher Education, the University of Limerick is still very heavily oriented towards industrial applications. The researchers in the Department of Materials Engineering and Industrial Chemistry interested in Air Force research programs were from the areas of ceramics, composites, polymers, biotechnology, and surface chemistry. Potential areas of interest for the Air Force were UV/V is spectral and conductance behavior of Langmuir--Blodgett films on semiconductors for sensor/detector applications, "engineering of plasmids" for biochemical detection, sintered silicon nitride processing chemistry and SiAlON oxidation mechanisms, and effects of contact with fluids; e.g., fuels on the flexural strength of composites.

Physical and Inorganic Chemistry at the University of Manchester, by LTC Chet Dymek, EOARD. (ll pp) [EOARD-LR-89-031]

Chemistry at the Universtiy of Manchester is significantly enhanced by its proximity to the University of Manchester Institute of Science and Technology (UMIST) and the Synchrotron Radiation Facility at Daresbury. There are collaborations and relatively easy access to a wide range of top notch facilities. The Physical Chemistry group is strongly focused on molecular beam type experiments with both gas phase molecular dynamics and surface reactions being studied. The Inorganic Chemistry group is also strongly focused on organometallics emphasizing the mechanism of operation of metalloproteins.

Physics

Composite Mirror Technology at SPACEFORSCHUNGSGRUPPE, Buchenbach, Germany, by Dr. Vince Donlan, EOARD. (5 pp) [EOARD-LR-89-014]

Dr. Wolfgang Ernst founded his own company, SFBF, to promote the technology of large graphite fiber reinforced composite mirrors made by replication from master negatives. In work done in collaboration with the Technische Hochschule in Darmstardt, SFBF have reported the fabrication of 1.5 and 2.4 meter diameter graphite epoxy mirrors with quarte-wave aluminized surfaces, using metal master negatives. To get more precise surfaces, up to 1/20 wave, Dr. Ernst next proposes to employ diamond coatings. This report provides some details of the current status of Dr. Ernst's work.

The Contraves Company, by Dr. Vince Donlan, EOARD. (4 pp) [EOARD-LR-89-015]

Contraves is an international company that specializes in air defense systems. Its current product line includes the Skyguard, Fieldguard, and Seaguard radar-controlled fire control systems, and the Gun King electrooptical gun control system. Contraves R&D oriented toward future improvements in radar-control and terminal defense includes sensor fusion, laser beam riders, target identification algorithms, and operator-aided tracking and target assignment.

Centrifuge 88 Conference, by LTC James G.R. Hansen, EOARD. (38 pp) [EOARD-LR-89-019]

An International Conference on Geotechnical Centrifuge Modeling was held under the auspices of the I.S.S.M.F.E. (International Society of Soil Mechanics and Foundation Engineering). The 3-day assemblage of centrifugists from around the world provided an appropriate forum for the dissemination of information. A brief outline of all the oral presentations as well as the majority of the special and general reports is contained in this document. In addition, a list of participants, and the table of contents from the Proceedings is included. This report was prepared by Dr. Bloomquist of the University of Florida for EOARD.

20th Europhysics Conference on Macromolecular Physics, by LTC James G.R. Hansen, EOARD. (8 pp) [EOARD-LR-89-020]

The central theme of the 20th Europhysics Conference on Macromolecular Physics was physical mechanisms in polymer failure. The topic was viewed from all possible levels and directions, ranging from the molecular scale of small deformations to the macroscopic behavior of fibre-reinforced composites. This report, written for EOARD by the conference organizer Prof Kausch, Swiss Federal Institute of Technology Lausanne, summarizes major recent developments as presented by invited lecturers.

Electromagnetic Device Research and Development at Tesla Engineering Ltd., by Dr. Vince Donlan, EOARD. (3 pp) [EOARD-LR-89-024]

Tesla Engineering Ltd., Storrington, U.K., designs and produces electromagnets and related devices for high energy physics, medical systems, and defense applications. They have

supplied magnets to the CERN and DESY electron synchrotrons and to Boeing for a free electron laser. They have designed magnets for the Princeton and Culham fusion laboratories, the European Synchrotron Radiation facility in Grenoble, and the Heavy Ion Accelerator in Darmstadt. They design and manufacture magnetic windings and tubes for NMR tomography equipment. They manufacture magnetic fuzes for torpedos. Currently, Tesla is attempting to extend their defense work into the areas of EM Launchers and neutral particle beam accelerators.

Semiconductors

Semiconductor Activities at University of Linz, by Dr. Eirug Davies, EOARD. (4 pp) [EOARD-LR-89-027]

The semiconductor effort at Linz is based on HgCdTe and GaAs. Hot walled epitaxial growth of CdTe on GaAs is used to provide substrates for mid i.r. detectors. These are now produced by a local company. Implantation and defect studies are undertaken in GaAs. An MOCVD system is used for producing field-controlled T E oscillators. Their present operation at 40 GHz is being extended to 90 GHz.

Advanced Composites in the BRITE/EURAM Program, by LTC James G.R. Hansen, EOARD. (33 pp) [EOARD-LR-89-026]

This report summarizes advanced composite projects presented at the BRITE/EURAM Technological Days, January 1989. Basic Research in Industrial Technologies for Europe and European Research on Advanced Materials are European Community (EC) programs concentrating on R&D to make European manufacturing industries more competitive in the world market. The 1989-1990 BRITE/EURAM program will be funded by the EC at $500 million. Information includes collaborators on significant advanced composite R&D programs funded by BRITE/EURAM.

CNET Laboratoire de Bagneaux, by Dr. Eirug Davies, EOARD. (4 pp) [EOARD-89-032]

The Bagneaux facility is one of the more research orientated laboratories of Center National d'Etudes des Telecommunications (Center). It provides support to France Telecom and its efforts are primarily directed at compound semiconductors. Optical sources and detectors for fiber communications are heavily emphasized. The Center can produce state of the art structures in both InP and GaAs and for optical fiber as well as other applications.

THE EMBASSIES: TECHNOLOGY ROUNDUP

France

For further information on France items, contact Dr. Allen Sessoms, Science Counselor, American Embassy, Paris, APO New York 09777.

The French National Center for Scientific Research

Background. The National Center for Scientific Research (CNRS) was created in 1939 and has served as the focus for French fundamental research ever since. It covers all scientific fields, and is the focal point for government-supported R&D. Funded by the Ministry of Research, the CNRS is a public establishment dedicated to scientific and technological research. It is endowed with financial autonomy and is civilian in character. Its missions, as set out in a 1982 decree, are as follows:

- Evaluate and effect research whose goal is to advance the scientific, as well as economic, social and cultural progress of France
- Contribute to the application and the exploitation of research
- Develop scientific information, favoring the use of the French language
- Contribute to education by and for research
- Participate in national and international scientific programs and evaluate their potential for development in light of national projects.

The general goals of the organization are refined into more explicit objectives for each area of scientific research. These are formulated at the department level and reflect short- and long-term research priorities. The head of the CNRS, the Director General, is responsible for designing and executing an approach (or "politique") that will promote financial, scientific, and social emphasis on meeting these goals. The politique is implemented at all levels of the CNRS hierarchy. In principle, the organization is decentralized, and regional administrators are responsible for encouraging local laboratories to do research in areas encompassed by the broad national approach. In reality, the system is cumbersome and bureaucratic and often reverts to one in which marching orders originate in Paris and are distributed as "edicts" throughout the CNRS system.

Each department is headed by a scientific director who insures that the laboratories and staff are working on projects conducive to furthering

departmental and thus CNRS objectives. The director allocates department funds to the laboratories within the particular field of study.

Organization of the CNRS. The CNRS is a hierarchical organization in which a Director General presides over seven scientific departments. The Director General is selected by the Minister for Research (Minister) and approved by the Council of Ministers (chaired by the Prime Minister). In general, the Director General comes from a field of well-known scientists. The Director General is responsible for managing the financial, scientific, and administrative policies of the CNRS. This essentially involves overseeing the seven scientific departments and distributing among them the general funds provided by the Ministry for Research. The current Director General, Francois Kourilsky (appointed July 1988), is a biologist and the first nonphysicist to hold the position. Kourilsky replaced Serge Feneuille who resigned after the French presidential and legislative elections.

Although the departments are distinct entities, there is some overlap of subject matter between them. The amount allocated to each is a rough indication of the relative importance of scientific fields:

The abbreviation following the department title is the one used by CNRS.

	MF	Percent
Life Sciences (SDV)	1,704	23.6
Chemistry (CHI)	1,056	14.6
Social and Human Sciences (SHS)	928	12.8
Nuclear Physics (PNC)	809	11.2
Earth, Ocean, Space Atmosphere (TOAE)	801	11.0
Basic Mathematics and Physics (MPB)	788	10.9
Engineering Sciences (SPI)	625	8.6

Note that even though life sciences and chemistry are at the top of the list, combining the departments of nuclear physics, basic mathematics and physics, and engineering sciences reveals that physics-related fields are the major priority at the CNRS, taking up some 30 percent of the budget (2222 MF).

The Laboratories. The CNRS-funded laboratories can be grouped into three categories: laboratories completely run by the CNRS ("laboratoires propres," L.P.S.), associated laboratories (L.A.S.), and mixed laboratories ("laboratoires mixtes," L.M.S.).

A "labo propre" is one whose rent, equipment, maintenance, and other associated costs are paid in full by the CNRS. Numbering around 300, these labs employ CNRS researchers, researcher/instructors ("chercheurs-enseignants") and other researchers from French or foreign universities, research organizations, or companies.

In addition, there are as many scholarship students working there as there are researchers. This type of laboratory is most commonly found on university campuses, but they remain legally and financially independent of the university. Alternatively, they may be part of a "groupe CNRS"; these research centers, composed entirely of L.P.'s, are scattered around France.

The most common type of laboratory is the L.A. Approximately 1,000 of these are located at the different French universities with which they are associated. There are some instances in which they are linked to other organizations. The LA's are units belonging to other organizations (mostly universities in the case of CNRS) asking to be associated with CNRS. In practice, associate units function as actual CNRS units and the borderline between both is not always obvious.

The mixed laboratory is the most interesting when considering the CNRS-industry relationship. As with the L.A.'s, the CNRS pays some variable part of laboratory costs. However, in an L.M., the responsibility for maintenance may be shared. The partner organization is most commonly a university (as in the case of the CNRS/Louis Pasteur University/Chemistry School L.M. known as the Institute for Material Physics and Chemistry). The collaborator may also be a government research organization (for example, the large Saturn synchrotron in a CNRS/CEA laboratory) or a private French company; i.e., the mixed CNRS/Rhone-Poulenc organic chemistry laboratory. The future growth in L.M.'s is expected to be an excellent means of extending and improving CNRS ties to industry. This prediction has been strengthened by the financial and political emphasis the Rocard government has placed on R&D in private French laboratories.

There is a fair amount of turnover among CNRS laboratories, especially among the associated laboratories. The possibility of losing part or all CNRS funding motivates researchers to maintain a high level of diverse, quality projects. Conversely, the rewards of being a CNRS laboratory are great enough to inspire competition among researchers.

Funding. The French government supports the CNRS financially. Of a 1987 budget of 8,899 MF, only 86 MF (or just over 1) came from the "CNRS resources"--the only non-government source of funds. The CNRS defines these funds as accruing from the sale of goods and services, excluding those contracts and subsidies that are budgeted over the course of the year. Excluding cutbacks made during the 1985-86 period, the CNRS has enjoyed a reasonably steady rate of budget increases, rising by 7.8 (in nominal francs) between 1986 and 1987. The CNRS budget accounts for about approximately 20 percent of the French government's annual civil budget for technological R&D. The Ministry of Research is responsible for financing CNRS expenditures. The Minister exercises this authority in two ways: a large part of the CNRS budget is turned over to the Director General who then allocates it to the scientific directors. The latter reapportions this money to his laboratories. The

remaining funds are given directly to the different scientific directors by the ministry with instructions to use them to promote research in specified areas of interest. These areas are determined by the Minister in consultation with his scientific advisors.

Up to 70 percent of the 1987 budget was used to pay personnel costs (5.6 BF) and administrative costs (202 MF). The remainder (2.1 BF) was distributed to departments to be channeled to individual laboratories and research teams.

For all laboratories, including the L.P.'s, additional funds may be provided by universities, other research organizations, French companies, and foreign companies or government organizations. The CNRS generally provides base funding ("soutien de base"), for equipment and financial endorsement for particular programs or projects ("ASIP" funds, which stands for actions d'intervention sur programme et actions incitatives, usually take the form of supplementary salaries for the researchers involved). Although the net amount provided will vary from department to department and from laboratory to laboratory, base funding is usually the largest component of the funds supplied. A laboratory may also benefit from very large equipment, but this is usually paid for by departments and shared among them.

Supplementary resources are usually project-specific, in contrast to the team-specific approach that generally characterizes French government funding for research. This differs greatly from the American research system, where nearly all spending is allocated to approved proposals from individual researchers. In France, it is the researchers (independent of proposals) and the research team or unit they work in that is government funded. Results are then evaluated with respect to CNRS (and hence national) objectives. Projects are frequently pursued without extensive consideration of their potential applications. An industrial partner intent on getting a return on a research investment can thus compensate for the limitations of the CNRS funding system.

The Relationship to Industry and the Application of Research. The CNRS (and indeed all French research organizations) constantly refer to "la valorization de la recherche." This overused phrase, translated as "the application and exploitation of research," has become the focus of the French effort to innovate. The CNRS naturally plays a major role in the Rocard government's initiative. More than 1000 enterprises work with CNRS laboratories through a number of different channels; structural ties with industry are diverse ranging from collaborative contracts to scientific groups. Sharing research and knowledge is further fostered by exchanges of personnel--be they internships for students, industry-financed research grants, the secondment of CNRS researchers to industry, or extensive consulting activities. In 1986, the CNRS developed personnel exchanges and partnership agreements with some 1500 firms; more than 650 collaborative contracts were signed for in excess of 110 MF (six times greater than the corresponding 1982 figure) indicating a sharp rise in common research projects.

An interview with a budget officer, revealed that mixed laboratories--those jointly funded by the CNRS and a public or private organization--are becoming a very significant means of improving ties to industry. Five new L.M.'s were created in 1986, and that the number has since increased. This trend will be further encouraged by the French government's emphasis on industrial research.

Despite all this activity, it appears as if CNRS links to the private sector--and hence its ability to convert research results into tangible, usable information and products--are limited, this is partially attributable to the fact that there is no French equivalent of venture capital. Companies are unwilling to sponsor public basic research programs for fear that they will be unable to use the results and compensate for short-term losses. Banks are similarly reluctant to give loans for research. The problem is not unique to CNRS, but because it is an organization geared to doing fundamental research, it tends to suffer heavily in this respect. The new government is trying to counteract this lack of industrial enthusiasm. France's growing realization of their serious innovation problems is largely responsible for the recent increase in cooperation between the CNRS and private enterprise.

International Cooperation. The CNRS is intent upon pursuing projects within the European community, with developing countries, and with large, industrialized countries such as the U.S. and Japan. This policy is pursued on four levels:

1. French researchers are educated abroad and foreign researchers in France
2. The exchange of researchers is incorporated into the framework on international agreements
3. Bilateral seminars and international colloquiums are organized to further international research
4. International scientific cooperative programs (PICS) and "actions thematiques programmees" such as ATP-Europe, ATP-US are created.

The prospect of a unified European market by 1992 has obliged the CNRS to begin developing the strong ties required for intra-European research. Its status as a government organization has enabled it to become well integrated into European public and private sector scientific actions. This applies to both government and private actions. For example, a EUREKA robotics projects involves collaboration between the CNRS and 10 French and European industries in terms of CNRS international priorities. In 1986, Europe featured more prominently than the U.S. for the first time. More cooperative agreements were signed with the Eu-

ropean countries than with the U.S. More significantly, there has been a greater increase in the number of cooperative agreements with European partners than with American partners. This is partially explained by the imbalance in financing exchanges of researchers. Nonetheless, the market potential in the U.S. and Japan and the desire to develop joint research facilities in poorer countries have been instrumental in determining how the CNRS expands abroad.

Objective comments on the CNRS international "politique" are hard to find. A pamphlet entitled "CNRS 1986" provides only numbers. Unfortunately, it is difficult to make more constructive predictions as to how the CNRS will change to adapt to the upcoming economic changes, or if indeed it will. One would suspect that the new Director General Francois Kourilsky has some ideas as to how to ameliorate CNRS effectiveness in this sphere and others.

The French Atomic Energy Commission

Background. The Commissariat a l'Energie Atomique (CEA) has a total budget of about 18,600 million francs (MF) (about $3,100 million) Of this, approximately 6,600 MF (about $1,100 million) is for nonmilitary research and development; thus, CEA is of global importance. Its research covers almost all fields of scientific endeavor, with an emphasis on nuclear and atomic physics, but with significant work being conducted in biology and medicine, materials, robotics, and chemistry. In the areas of CEA's competence, they are probably the most important international partner. United States researchers enjoy close contact with their CEA counterparts. This article draws extensively on the work of summer intern Alexandra Vacroux from Tufts University.

The CEA was created in 1949 as part of the French government's effort to recuperate from World War II.

The prestige of nuclear energy resulted in the CEA being considered a symbol of "reconstructing a genuinely French technological and scientific capability." To this extent, it has been successful; nuclear energy provides France with 70 of its electricity needs. The problem the CEA now faces is one of a nearly exhausted French market; other markets are being explored as substitutes, most notably those of Pakistan, India, China, Japan, and the U.S. Understanding the CEA's structure and objectives is important if we are to appreciate some of the Government of France's initiatives in CEA's areas of competence. The basic objective of the CEA is to further French knowledge of nuclear energy and to exploit this information in industry. Initially designed to cope exclusively with nuclear energy and its applications, by 1970 the CEA had become larger than the size justified by the nuclear industry alone. In response, the French government passed an act allowing the CEA to engage in research and development in non-nuclear fields. This action permitted the CEA to exploit the technology stemming from nuclear energy in other fields such as electronics and computer technology, robotics, biomedical engineering, agriculture, materials, and energy control. Consequently, a fair amount of the research done in CEA laboratories and industrial subsidiaries is of a non-nuclear nature.

A percentage breakdown of the 1987 fundamental research budget of 1,800 MF provides an indication of CEA research priorities:

Condensed matter & atomic physics	26.0
Nuclear physics	21.5
Plasma physics & controlled fusion	21.5
Elemental particle physics	16.4
Physics of cosmic rays	5.1
Chemistry & physical Chemistry	3.8
Metallurgy	2.6
Theoretical physics (mathematical physics)	1.9
Geophysics	1.2

Organization of the CEA. The General Administrator and the High Commissioner hold the most important positions. Both are appointed by the Government's Counsel/Council of Ministers, and the CEA maintains that the two are equals. Although ostensibly true, it is in fact the General Administrator (G.A.) who is responsible for administering the CEA. A civil servant with a scientific background, he oversees both the research and industrial programs of the CEA. The G.A. is the strategist for the organization, thus is responsible for designing and executing the CEA's "politique." In a budgetary context, this means that he holds the CEA pursestrings.

The High Commissioner takes care of the day-to-day functioning of the CEA. He is the real scientific representative within the administration whose main responsibility is to manage the four CEA research institutes--the Institute for Fundamental Research (IRF), the Institute for Industrial Development (IRDI), the Institute for Protection and Nuclear Safety (IPSN), and the Directorate for Military Applications. The institutes are the bodies through which all CEA research is done. They are each minihierarchies headed by the High Commissioner who appoints four delegates to manage them. These representatives supervise the laboratories.

Funding. The CEA obtains funds from the government and from its own resources; i.e., consulting, royalties. The 1987 budget of 18,600 MF was 84.6 percent government subsidized (15,700 MF) and 15.4 percent self-provided (2,900 MF). The budget (and the CEA as a whole) is divided into two areas: civil and military, nearly equal in size. They differ in source contribution: the civil budget is about 71 percent government subsidized while the military budget is 99 percent government funded. This difference is understandable; the military R&D results are provided almost exclusively for the Ministry of Defense. The subsidy to CEA military applications was 4.31 percent of the total military budget. A percent-

age breakdown of CEA government-sourced expenditures reflects the importance of military R&D and nonmilitary R&D priorities:

Military applications	52.1
Nuclear programs	19.4
Fundamental Research	12.9
Innovation and exploitation of research	6.7
Protection and nuclear safety	6.1
Common interest programs	2.8

The Ministry for Industry and the Ministry for Research and Technology provide the funds for the General Administrator, who reapportions them to the different research institutes. The directors of the institutes then give the funds to the laboratories and researchers within their purview, who are budgeted according to the proposals they submit. In turn, consistent with project objectives, the researcher in charge has reasonable flexibility in spending his research funds.

A research proposal is, theoretically, evaluated according to the following procedure: a laboratory submits a proposal to the director of its institute who then presents it to the relevant High Commissioner delegate. This person evaluates and ranks the various proposals submitted and then distributes the funds to the researchers whose proposed projects best coincide with the CEA's broad national and international objectives. Before and during this process is the setting of the research plan, which is formulated by the High Commissioner and the GA in consultation with the industry. This effective process means that research is highly programmed.

Laboratories can also be funded by sources outside of their institutes. If another institute is interested in a particular project, it may allocate funds to the laboratory; e.g., the Institute for Military Applications could finance a program carried out within the Institute for Fundamental Research. Apparently, this cross-funding happens fairly often. Alternatively, other public or private organizations in France or abroad can support projects that interest them. The only exception appears to be the Institute for Military Applications. On the other hand, the Ministry of Defense has been known to finance researchers in other institutes.

The Relationship to Industry and the Application of Research. The CEA, a public organization, does or commissions all of the research needed by the nuclear industry. This industry, however, is comprised of CEA subsidiaries. Between 40 and 50, these subsidiaries known collectively as "CEA Industrie" are largely responsible for the exploitation of CEA research. Their specialties fall into six broad categories: fuel cycle, nuclear reactors construction and services, engineering, data processing service, biomedical, and other. The two largest subsidiaries are Framatome, which builds the nuclear reactors, and Cogema, the main fuel cycle company.

The main client of CEA-Industrie is Electricite de France (EDF), a government-owned monopoly. Thus, everything a CEA industry could want--research and development facilities and an assured client--is provided by the French government.

Non-CEA-affiliated industries can also benefit from CEA research. Laboratories within each institute (except for military applications whose client is almost exclusively the Ministry of Defense) can be contracted to do specific projects by French or foreign, public, or private organizations. Similarly, CEA industries can set up contracts with non-CEA research organizations.

Because the CEA maintains such a close relationship between research and industry, a truly effective policy of exploiting results requires that unrelated companies also apply CEA knowledge. This is effectively done on both national and international scales. In 1987, the CEA had two major international successes in this realm. SGN, a CEA-Industrie subsidiary, signed a contract with the Japanese National Fuel Society. In addition, an accord was signed that permits marketing of French technology in the U.S. in the area of nuclear fuels. Agreements of this nature are very favorable for the CEA, and the American market is a prime target for future commercial activities.

International Cooperation. The CEA, having nearly exhausted the French market for reactors and other nuclear accoutrements, is concerned with finding new markets. This search logically encompasses three types of countries: large industrialized, smaller European, and developing countries. Although the first may be more promising in this long run, the CEA has found that the American market is difficult to penetrate.

The American market is restricted for two reasons. First, the U.S. has a developed nuclear research and industrial sector of its own. Most of the work done by the French is or can be affected in the U.S. without French support. Projects or programs that cannot be executed by American companies are pursued on case-by-case basis. Another technique used for cooperation involves creating subsidiaries by French and U.S. companies; this was done in the case of Babcock & Wilcox Fuel Co. (created by Babcock & Wilcox, Framatome, Cogema, and Pechiney) and Numatec.

The U.S. government also cooperates with the government of France through agreements with the CEA. In 1987, four accords were signed: for CEA/DOE cooperation in R&D on fusion (May); and CEA/DOE accord on exchanges of energy information (July); CEA/EDF/Framatome/EPRI (Electric Power Research Institute) agreement on the study of combustibles; and a CEA/DOE agreement on research into protective measures for telemaintenance equipment. In 1989, another agreement for cooperation in the civilian aspects of inertial confinement fusion was signed.

The CEA civil part of the European strategy seems to be better formulated. The unified European market of 1993 will, in principle, provide easier access to the market of other European countries. This facility will be further encouraged if the other members of the EEC accept the French argument that nuclear energy is a prerequisite for a technologically independent Europe.

In terms of a general strategy, the CEA is well aware of the lessons of Chernobyl that demonstrated the importance and international dimension of public opinion on nuclear energy. The organization holds the expected international conferences. In August 1987, the CEA and its subsidiaries displayed their technology and scientific acquisitions to 640 conference participants from more than 23 countries.

To put the international and national approaches into perspective, one can examine the following data from the CEA annual report:

Partners	Nr End 1986	Signed In 1987	Nr End 1987
Public French Organizations	63	14	73
Public Foreign Organizations	78	10	6
French Industry	201	21	207
Foreign Industry	34	3	36
CEA Group Members	79	19	82
Small & Medium Businesses	231	50	264
Total	686	117	726
Non-nuclear	328	83	368

The CEA has been a major success story for France. It has made the French the leaders in Europe in nuclear energy and has had a major impact on the world market. Its challenge for the future will be to maintain this preeminence and to redefine its role as a European one as the Economic Community approaches 1993.

France's Zeus Airborne Electronic Warfare System

The chances of the Marconi Defense Systems (MDS) Zeus integrated electronic warfare (EW) system being considered for use on the U.S. Marine Corps' (USMC) AV-8B Harrier II have brightened, following a Foreign Weapons Evaluation (FWE) bench trial undertaken at the US Navy's Pacific Missile Test Center, Pt. Mugu, California, earlier this year.

Following the trial, the USMC noted that the equipment completed the test period without failure; that the system met its performance specification in all respects; that it was capable of correctly processing the most complex scenarios that the test facility could generate; and that the system could be effectively integrated with the AV-8Bs existing ALR-67 antenna and cockpit units for the warning function.

As result, MDS expects a full-scale FWE flight trial to take place over the U.S. Navy's EW range next year. Procured by the RAF for use in its Harrier GR5/7 aircraft, the Zeus program aims to provide an integrated warning/electronic countermeasures (ECM) capability suitable for use in the Central European threat environment.

Work on Zeus began in August 1983 when MDS was awarded a development/production contract for the system. Preproduction examples appeared in early 1987 with production units following in the latter part of that year. The MDS stresses both the speed at which it has developed the system and the fact that to date, all major contractual milestones in the program have been achieved on schedule.

In the Harrier GR5 installation, Zeus comprises seven line replaceable units (LRUs)--receiver, video signal demodulator (VSD), data processor unit (DPU), power supply, techniques generator (TG), and two transmitters--served by four transmission and eight reception units. All the LRUs, apart from one of the transmitters, are mounted in the aircraft's fuselage avionics bay, while the various antennas are located in a ventral fairing under the nose, in wingtip installations and in the extreme rear fuselage. The complete installation weighs under 200 kg, has a volume of approximately 0.12m(3), and a power requirement, "in normal configuration", of 4kVA.

In the GR5/AV-8B, the pilot/system interface is through the aircraft's general purpose display (GPD) cathode ray tube and its soft key controls.

Threat data can be displayed on this unit, via the head-up display (HUD), through a series of warning lights and in aural form, depending on the pilot's particular mission requirements.

Zeus's warning subsystem detects pulsed and continuous-wave threat signals in the C- to J-bands through separate HI- and LO-band antenna arrays, covering 360 degrees in azimuth and plus/minus 45 degrees in elevation.

The receiver used is of the multichannel superheterodyne variety with an instantaneous frequency measurement capability. Acquired signals are passed from the receiver to the VSD where a range of parameters are measured and digitized for onward transmission to the DPU. Known parameters measured include direction and time-of-arrival, frequency, pulse repetition interval, pulse width, pulse amplitude, and scan type/rate.

The DPU automatically identifies the threat, generates the threat display, selects the appropriate countermeasure option, and interface with external systems (in the Harrier GR5, the Plessey missile warning radar and an undisclosed chaff/flare dispenser). For threat identification and prioritization purposes, the DPU contains a threat library that typically holds details on 1000 emitters. Threat classification is by radar type, the weapon system it relates to, its bearing relative to the aircraft, and its amplitude (that is, whether it is locked on).

In presenting this to the pilot on the GPD, the DPU interfaces with the aircraft's navigation system (via the 1553B avionics bus) both to enhance

the accuracy of the bearing information and to slave the display to the aircraft's heading and attitude.

The MDS claims that this ability to talk to a navigation system is unique in an airborne EW system. If active jamming is the chosen defensive option, the DPU passes signals to the TG for selection of the appropriate mode necessary to counter the specific threat. This is reportedly accomplished with "a high degree of fidelity." The DPU software is written in high level CORAL66 and is divided into "housekeeping" (control, calculation, and input/output algorithms) and "operational" (control and dynamic data) modules. This approach has been taken to simplify reprogramming for new or changing threat environments and system installation in varying platforms.

The DPU memory is described as "large, with the capacity for enlargement to meet future threats." Software flexibility is matched by hardware with the system capable, for example, of being rigged for the warning function only (by removing the transmitters) or for "dispersed installation", that is, with the warning function carried in one aircraft and the jamming function in another, the two connected by a data link. Active jamming modes available on Zeus include spot noise, velocity gate pulloff, deception, and cooperative (anti-monopulse).

The transmitters employed are Nothrop designs based on the company's bid for the U.S. Airborne Self-Protection Jammer program. The MDS describes them as being the "world's most efficient compact transmitters", and in a move obviously aimed at U.S. market penetration, the two companies have signed a cross-license agreement on Zeus.

Zeus is completed by a wide range of support facilities, beginning with a builtin test (BITE) function. All the suite's LRU's are modular in design and any BITE-indicated failure can be identified to LRU level on the flightline using the system's ground program loading unit's ground test maintenance program.

Necessary software data and algorithmic changes are run through both an EW simulation facility and a validation rig before being incorporated into preflight message tapes (in cassette form) for operational use. The ability to effectively modify Zeus software is particularly important in view of the system's projected 20-year operational life.

While the present emphasis is on the Harrier II family, MDS stresses Zeus's suitability for other aircraft types such as the F-16, F/A-18, F-5, A-4, Mirage, and Jaguar. The company is bidding Zeus for the integrated ECM system on Turkish Air Force F-16s. Of the above aircraft, work on an F-16 installation is the most advanced. The MDS and General Dynamics have completed the necessary design work for a Zeus application to the C- and D-model Fighting Falcons.

The Medical Research System in France

Introduction. The public medical research sector includes public research institutions as well as universities and hospitals. For the purpose of this report, the semipublic sector--comprised of private state-approved foundations that are partially state-financed--is also included. Public research institutions are organized along the same general lines but we will also point to their differences. Except for nonprofit organizations, research institutions are essentially state-financed and their personnel are civil servants. For the most part, they have all defined ways to interact more closely with industry.

Public medical research in France cannot be dissociated from the general French public research system. Therefore, it is necessary to briefly describe the latter in order to understand how the former is organized.

The Public Research System in France. The public research system in France is unique among OECD countries. In other countries, universities tend to be the central focus of nonmilitary government sponsored research. In France this responsibility lies principally with a certain number of relatively autonomous public institutions with overlapping jurisdictions. This results in a complex structure, making policy coordination cumbersome while increasing the number of financial sources.

The major reason for this situation is historical. After World War I, the shortcomings of French universities prevented the development of a modern public research system. The first public multidisciplinary research institution, the Centre National de la Recherche Scientifique-National Center for Scientific Research (CNRS) was created in 1939 in response to French universities' inability to coordinate or conduct research. The CNRS established laboratories independent of the universities. Certain laboratories were associated with universities which meant that staffing and facilities were shared. Initially aimed at basic research, the CNRS gradually expanded its activities to include applied and goal-oriented programs. The CNRS grew in importance after World War II to become the principal public research institution in France. At the same time, numerous other public institutions were born, specialized in one or several fields of science (medical, atomic energy, agriculture). However, public law confined public research institutions to research functions. Interaction between research agencies and with industry was low. The program law of July 15, 1982, for research and technological development modified the structures and responsibilities of public research institutions. Two categories of institutions were created: EPST (Etablissement Public a Caractere Scientifique et Technique - Public Scientific and Technical

Institution) and EPIC (Estblissement Public a Caractere Industriel et Commercial - Public Industrial and Commercial Institution). This structure makes a distinction between a more basic research sector (EPST) and a more industry-oriented applied sector (EPIC). This law extended the functions of the public research institutions which may now include the exploitation of research, the dissemination of scientific and technical information, and training. The basic difference between the two structures is that EPST's are governed by general civil service rules: e.g., their staff are civil servants and are subject to prior control of expenditure. EPIC's personnel are governed by regulations that resemble those in force in the private sector and are not subject to previous control of expenditure. This makes EPST's less flexible and less responsive to rapidly changing circumstances than EPIC's. Examples of each will be given later.

Organization of Public Medical Research in France. Publicly supported medical research in France falls within the general framework of public research but is distinguished by two unique features. First, universities are closely connected with hospitals. The second distinguishing feature is that, besides public research institutions and universities, a third grouping exists that we shall call semipublic. The public medical research system in France therefore comprises three sectors (public sector, semipublic sector, and hospital university sector).

It is also worth mentioning that, at the initiative of President Mitterand, a National Ethical Committee for Life and Health Sciences was created in 1983 and placed under the joint authority of the Minister for Research and the Minister for Health. The National Ethical Committee is responsible for advising on moral problems raised by research in biology, medicine and health, whether these problems concern human beings, social groups, or society as a whole.

The Public Research Institution Sector. The public research institution sector is almost entirely state-financed. The CNRS and Institut National de la Sante et de la Recherche Medicale-National Institute for Health and Medical Research (INSERM) are the main organizations in the system. However, there are other public institutions which are also involved in medical research: Institut National de la Recherche Agronomique - National Institute for Agronomic Research (INRA); Commissariat a l'Energie Atomique-Atomic Energy Commission (CEA); and Institut de Recherche Scientifique pour le Developpement en Cooperation-Scientific Research Institute for Development in Cooperation (ORSTOM).

The CNRS is the largest French public research institution and covers all fields of science. It includes seven scientific directorates. The Life Sciences Directorate is responsible for research in health, agronomy, food, nutrition, and biotechnologies. The Life Sciences Directorate in turn includes 11 sections, two of which (Sections 27 and 28) are more specifically oriented toward biomedical research.

Section 27 covers experimental pharmacology and therapeutics, including:

- Molecular, biomedical, and functional pharmacology
- Pharmacokinetics and metabolism of medicines
- Therapeutic chemistry
- Toxicology
- Experimental therapeutics
- Medical and biological engineering

Section 28 covers experimental and human physiopathology, including applied physiology, ergonomy, work pathology

- Human genetics and cytogenetics
- Immunopathology
- Metabolic and nutrition physiopathology
- Carcinogenesis, mutagenesis
- Molecular and cellular physiopathology

In addition, two other directorates support biomedical research. These are the Chemistry Directorate for Biological and Therapeutic Chemistry and Physical Chemistry, and the Directorate for Engineering Physics for Instrumentation and Biological and Medical Engineering.

The INSERM, created in 1964, replaced the "Institut National d'Hygiene" (National Institute for Hygiene) created in 1941. It is the only public institution that specializes in medical and health research. Research is focused on three main lines:

- Research in normal and pathological molecular and cellular biology and biophysics
- Research in the five main systems or functions: immunology; reproduction and development; cardio-vascular, respiratory, renal and urinary systems; nervous system including sensory organs; and metabolism
- Research in public health, epidemiology, and health economics.

In addition to these priorities, INSERM is responsible for conducting any other necessary medical or public health research.

INRA, created in 1946, specializes in agricultural research. It is comprised of six scientific directorates two of which are involved in medical research--Animal Production Directorate and the Food and Nutrition Directorate. Only three research departments in the Directorate for Animal Production conduct research connected with the medical field--Animal Genetics, Animal Physiology, and Animal Pathology; and one research department in the Food and Nutrition Directorate--Consumption Sciences (study of glucides, lipids, and proteins).

The CEA, created in 194., is responsible for promoting the use of nuclear energy in science, industry, and national defense. It owns industrial

firms in the nuclear energy area and conducts France's nuclear weapons program. In addition, the CEA conducts research in radiological protection and radiotherapy.

Medical research is conducted by the Mission for Life Sciences and Techniques, including

- Basic research: Biology (Biophysics, Biochemistry, Cellular Biology)
- Applied research: Engineering of the processes in the food and nutrition area, using radiation, using micro-organisms for bioproduction of high value-added molecules.

ORSTOM, created in 1943, is responsible for promoting and conducting research on the physical, biological, and human environments of developing countries. The Health Directorate is responsible for developing knowledge and strategies that can help control diseases that primarily affect third world countries. Research includes biomedical research, the study of nutrition-related diseases, the socio-economic factors contributing to health, as well as the anthropological representation of the disease.

Under the Ministry for Research and Technology, CNRS, INSERM, INRA, and ORSTOM are EPSTs while CEA has a unique status that is close to that of an EPIC. Because of its extensiveness, CEA has been characterized as a "public scientific, technical and industrial research and development establishment." However, all but the CNRS, also have other supervisory authorities. The INSERM also is under the Health Ministry; INRA under the Agriculture Ministry; CEA under the Industry Ministry, Defense Ministry and Prime Minister; and ORSTOM under the Cooperation Ministry.

The Semi-Public Sector. The semi-public sector is partially state-financed, and includes two private state-approved foundations, the Pasteur Institute, and the Curie Institute, both named after their respective founders.

Their status enables these non-profit foundations to receive private legacies exonerated from inheritance tax as well as donations that are partially tax deductable. Businesses may also deduct from their incomes part of their contributions. Because they are only partially state-financed, state-approved foundations have more latitude for independent action than public institutions.

The Pasteur Institute, created in 1886, is the main private, state-approved foundation in the medical research sector with no equivalent in the world. The Pasteur Institute is a center for basic research--microbiology, virology, immunology, molecular and cellular biology; for research applied to human and veterinary medicine, to hygiene, public health, agronomy, and industry; a center for post-university teaching; and a hospital specializing in parasite and immunological pathology. Also included are libraries, two museums, and a documentation center. The Pasteur Institute in Paris is at the center of a network of other Pasteur Institutes: in France--Lille and Lyon; in the French overseas departments and territories--Guaeloupe, New Caledonia; and abroad--Greece, Tunisia, Algeria, Morocco, Senegal, Madagascar, and Kyoto, Japan.

The Pasteur Institutes based overseas conduct research programs that meet the specific requests of host countries and are in keeping with the recommendations of international organizations. This network of institutes spread around the world has remained, 100 years later, unique and has largely contributed to the reputation of the Pasteur Institute.

The Curie Institute resulted from a merger in 1970 of the Curie Foundation--a hospital created in 1920 -and the Radium Institute, which was a research institution. The Curie Institute concentrates exclusively on cancer research and treatment as well as on research on the action of ionizing radiations on normal and pathological tissues (radiobiology).

The University and Hospital Sector. Medicine has a specific place within the university since it belongs to both the hospital and the university. Contrary to other disciplines, it has a threefold mission: research, teaching, and treatment. This mission was clearly defined in an ordinance of 1958 that provided for the creation of the Centre Hospitalo-Universitaires-Hospital and Univesity Centers (CHU) and officially confirmed that medical research should be conducted within hospitals. Hospitals that signed conventions with universities acquired the status of CHU. A law of 1970 extended the responsibility to conduct research to all hospitals, regardless of whether such conventions. Besides university research units, laboratories from public research agencies are also located on the CHU premises. Relations between the various institutions are complex and often confusing even for the hospital and university management officials. Research conducted within universities and hospitals will be the subject of a special section in this report in view of the specific problems that the system generates.

Management Structure of Head Offices. The CNRS is the largest French multi-disciplinary public research institution. The diversity of its activities, its size, and the existence of several directorates naturally encourages a bureaucratic structure. The CNRS Life Sciences Director must refer any major policy decision to the CNRS Director General. In contrast, the INSERM Director General is the highest authority within his organization. For example, when a reform appears necessary within the CNRS Life Sciences Directorate, it must be applied across-the-board to all other directorates where it may not be appropriate. Consequently, life sciences specific reform is difficult if the problem addressed is not inherent in the organization. The INSERM

can adjust more rapidly than CNRS to changing circumstances since it is oriented wholly toward biomedical research. The INSERM is also a younger organization and thus has been able to avoid some of the mistakes made by CNRS and to develop a more responsive organization.

All public medical research institutions are organized along the same broad lines. They include a governing board, a director general, a scientific council, scientific commissions, and functional directorates. The governing board, responsible for the administration of research institutions, is chaired by a French government cabinet nominee and consists of government representatives (8 at INSERM, 3 at CNRS), representatives of the economic, research and development, or labor world (12 at INSERM and CNRS) and staff representatives (6 at INSERM, 4 at CNRS). The Director General who manages the institution is also a cabinet nominee. Thus, the institutions are sensitive to political realities. The organization of CEA is somewhat different but ensures responsiveness to governmental concerns as well. The Pasteur Institute is also run by a governing board, which nominates the managing director. An assembly composed of 100 persons elects the members of the board that also includes, besides elected members, government representatives as well as representatives of both INSERM and CNRS. The same is true of the Curie Institute. The role of the government, especially in all budgetary concerns, is clearly evident in spite of the same public status of both institutes.

The scientific council exists in most organizations. The council is an advisory authority that helps define and coordinate the scientific policy of the institution to which it is affiliated. The scientific commissions have an advisory capacity and are designated by research field and subject area. Each commission usually has approximately 25 members--half elected, the other half appointed by the administration. Because of the appointment procedure, they are not exempt from political pressures. They evaluate laboratories and researchers; participate in the recruiting and promoting; and review proposals to open, extend, or shut research units. At CNRS, the organization is slightly different. The "Comite National de la Recherche Scientifique" (National Committee for Scientific Research) is the authority in charge of both advice and evaluation. It is composed, inter alia, of 45 sections by disciplines and of a scientific council.

The various functional directorates are responsible for the exploitation and application of research; scientific information; international relations; training through research; and other administrative functions.

All public and semipublic institutions conform with the general pattern described above. However, ORSTOM, the Pasteur and Curie Institutes have special features that distinguish them from the other institutions. The ORSTOM teams, because of the institute's mission, principally work overseas (either in ORSTOM centers or in collaboration with the national institutions of partner countries) where the ORSTOM staff constitutes what is termed "ORSTOM outposts." It is expected that ORSTOM centers will gradually be absorbed into the infrastructure of the host country, since the third-world countries concerned have become independent. The ORSTOM researchers are present in some 40 countries. In each of these, ORSTOM appoints a representative who is responsible for transmitting the requests of ORSTOM partners to the central organization and for ensuring that the program is carried out in compliance with cooperation goals.

The Pasteur Institute has nearly 80 research units grouped into 9 departments. Included is a hospital, reference centers, and a teaching center, and is characterized by the existence of a worldwide scientific community. The Pasteur Institute Hospital, created in 1900, was the first hospital in the world to isolate patients with infectious diseases. The Pasteur Hospital presently specializes in the treating infectious and parasitic diseases, mycoses, and diseases resulting from immune dysfunction. In France, it ranks third in hospitalization of AIDS patients. The Pasteur Institute also houses 14 of the 32 national reference centers in France, and 9 centers that collaborate with the World Health Organization. The purpose of the reference centers is to play both a preventive and advisory role in epidemiological surveillance and diagnosis. The Pasteur Institute also carries out post-university training in research and diagnosis. The Pasteur Institute welcomes nearly 300 students, both French and foreign, each year.

The Pasteur Institute in Paris is at the center of a worldwide network of 28 institutes. Included are the Pasteur Institutes per se which are the six institutes that are administratively, financially, and technically dependent upon Pasteur Paris (point-a-Pitre, Cayenne, Noumea, Bangui, Daker, and Madagascar). The others are institutes located in the host countries that enjoy preferential scientific relations with Pasteur Paris; e.g., Algeria, Ivory Coast, Greece, Italy; associate institutes that signed general scientific conventions with Pasteur Paris; and finally, institutes that signed agreements on specific joint programs. These overseas institutes are pursuing public health activities and conducting research. In coordination with Pasteur, priority research programs have been established; e.g., malaria, leprosy, rabies. The cooperation policy is the responsibility of Pasteur Paris and is either centralized when needs are of general interest or decentralized when needs are local. The Curie Institute is composed of three sections: a hospital for cancer treatment; the chemistry and physics section specializing in research on

radiology; and the biology section conducting research on radiobiology and carcinogenesis. Approximately 60 percent of the researchers' activity is devoted to cancer research and 40 percent to basic research; e.g., biological effect of radiations, molecular genetics, cytogenetics, immunology.

Regional Policy. For historical reasons, France is a centralized country and, consequently, public medical research institutions are concentrated in Paris. However, attempts are underway to decentralize. The CNRS is administratively decentralized in all regions of France. A regional delegate who represents CNRS provides for two-way information flow and promotes cooperation between the CNRS and the region. However, the CNRS Life Sciences Directorate still is poorly represented in the regions, particularly in Western France, with 55 percent of its activity is concentrated in the Paris area. The directorate is preparing a project in conjunction with the Ministry for Education and with universities in the various French regions. Even so, this directorate is less centralized in Paris than is INSERM. The INSERM has developed policies to remedy this situation. At both the scientific and administrative levels, INSERM is supported by 18 regional administrations. The Conseils Scientifiques Consultatifs Regionaux-Regional Scientific Advisory Consultants (CSRI) assists INSERM develop in their regions. The INSERM is about to sign (or has already signed) general agreements with many of them that define ways to cooperate; i.e., through information exchange and support of research. The INRA research centers and units about 300) generally pursue national (and sometimes regional) objectives. The ORSTOM has two major centers in France. One, located in Montpellier, conducts medical research that cannot be carried out in the developing countries (such as molecular biology). The CEA conducts basic and applied medical research in Grenoble, Fontenay-aux-Roses, Saclay.

Pasteur Paris has two branches in Lille and Lyon. They are administratively independent of Pasteur Paris but enjoy scientific exchange with the latter as well as with the Pasteur community as a whole. The Curie Institute has no regional representation.

Organization and Functioning of Research Units. The description of the organization of research units will help in understanding how these function.

Organization of Research Units. In general, both INSERM and CNRS possess research units that are administered by one organization only, and research units that are associated according to various formulas. There are also what is referred to as "Joint Service" units which carry out a function of general interest; i.e., data-processing, electronic microscopy. As of January 1, 1986, INSERM had 236 INSERM-administered research units and 13 Joint Service units. The CNRS Life Sciences Diorectorate had 42 CNRS-administered research units in 1987 and 7 Joint Service units. Although INSERM- and CNRS-administered laboratories come under one organization (INSERM or CNRS), they may house researchers from other public research institutions and universities. For example, at INSERM, only about half of the staff working in each research unit actually belongs to INSERM. Further, many units (about 50 percent at INSERM) are located on university or CHU premises. The INSERM tends to have more small units (staffed with about 30 people), while CNRS tends to have larger laboratories.

The formulas designed to associate other research institutions vary at INSERM and CNRS. The CNRS Life Sciences Directorate "associate units" and "mixed units." Associate units (224 in 1987) are units belonging to other organizations that ask to be associated with CNRS. In most cases, university units are associated with CNRS. The Pasteur Institute also has units associated with CNRS. In practice, associate units function as actual CNRS units and the borderline between both is not always obvious. Mixed units (10 in 1987) are units that are run by several organizations. There are mixed units with universities and some with INSERM. The INSERM has no associate units and has mixed units with CNRS only. It created a different procedure, called the "external research contracts." Such contracts are signed with teams who do not belong to INSERM (universities, other research institutions). In general, these are 3-year contracts that amount to approximately F100,000 ($16,667) per year (see footnote 2) . Such contracts are competitive; INSERM calls for proposals out of which only about one third of the applicants (about 160 to 200 projects) are selected each year. The INSERM supports about 500 teams through such contracts. For 1988, INSERM has developed a new contractual formula, the "young teams' contracts." They constitute an intermediary stage between actual research units and external research contracts. They have a 3-year duration that can be extended to four years. The INSERM will allocate a maximum of F250,000 ($41,667) per year and per contract. In 1988, INSERM opened 12 such contracts.

Finally, a last structure permits researchers to meet and exchange points of views. These are the CNRS Research Groupings (Groupements de Recherche) and the INSERM Clinical and Public Health Research Networks (Reseaux de Recherche Clinique et en Sante Publique). There are only a few of these at CNRS. At INSERM, some 30 networks are created each year. Currently, here are approximately 90 such networks. These were created to promote cooperation between researchers and medical practitioners. Selected through calls for proposals, they may not exceed 3 years and are allocated a maximum of F250,000 for expenses incurred to establish the

network. They are administered by INSERM and the other organization concerned; e.g., hospital, university, region, industry. Each year, over 130 teams of practitioners are associated, for a 3-year renewable period, with some 60 INSERM research units.

At INRA, there are 22 regional research centers, each beinging together on the same site laboratories responsible to various different departments. The INRA's laboratories are located in agronomic and veterinarian higher education establishments and in some at CEA, biomedical research is organized differently depending on whether it is basic or clinical research. Basic medical research is conducted within a federation of 10 biological laboratories associating CEA, CNRS, INSERM, and Universite Scientifique, Technologique et Medicale de Grenoble-Grenoble Scientific, Technological and Medical University (USTMG), located at the Nuclear Research Center of Grenoble. The Nuclear Research Center at Saclay also conducts basic research in renal and nervous system physiology. Clinical research is conducted in conjunction with CNRS and INSERM researchers, within the Frederic Joliot Department of the Orsay Hospital (physiology and pharmacology) whose technical equipment is unique in Europe. Clinical research is also conducted at the Saclay and Fontenay-aux-Rose nuclear research centers. The ORSTOM has research units and specific structures that conform with the mission of the Institute. These consist of ORSTOM personnel who are individually incorporated in various scientific institutions of ORSTOM partner countries; or who are grouped in one institution of the partner country and constitute an ORSTOM outpost. In addition, ORSTOM also has its own research centers but no associated laboratories. The ORSTOM Health Department has 9 research units whose 59 teams work in 25 countries in Africa, Asia, Latin America, and the Pacific, but is primarily present in tropical French-speaking Africa. In the partner countries, ORSTOM works with the host government universities, with whatever research structure exists there, with the host government health ministry and other ministries as necessary, and with international organizations such as World Health Organization and interstate organizations. As mentioned above, the Pasteur Institute in Paris numbers close to 80 research units. Many of the best Pasteur Laboratories are in some way associated with CNRS or INSERM. At the Curie Institute, research is conducted by units depending either on INSERM or CNRS. There are 12 research units, 7 belonging to CNRS and 5 to INSERM.

Functioning of Research Units. For illustrative purposes, in this section we focus on INSERM. Every year, INSERM initiates a call for proposals for the creation of research units. Themes reflect the priorities defined by the institute. In its effort to decentralise its activities, INSERM has ruled that two-thirds of the new laboratories would be created outside of the Paris area. Therefore, not only the proposal submitted by, but also the location of the applications are considered for the final selection. Four full-time researchers belonging to a public research institution, two of whom belong to INSERM, must be part of the team submitting an application. The rhythm of creation has risen from 5 new units each year in the early 1980's to 15 in 1986.

The unit is evaluated every 4 years by the appropriate specialized scientific commission. The evaluation may lead to the closing of the laboratory, with an average of about 10 units closing each year. Another reason for closing a laboratory is the 12-year rule. No one may run a unit for more than 12 years. Therefore, if a new director is not appointed at the expiration of this period, the laboratory is automatically closed. However, in practice, the retiring director may present a project to create a new unit, which is a way to bypass the 12-year rule. Although, by doing so, he then enters into competition with other teams. At CNRS, the 12-year rule also exists but is applied with flexibility. The CNRS units are created for four years (renewable). At CNRS and Pasteur Paris, laboratories are also assessed every four years but are subject at CNRS to a minor review after two years. There is a tendency to close more and more laboratories at INSERM, and begins to be true for CNRS. Since 1984, 38 laboratories have been closed at INSERM while only 5 were closed between 1979 and 1984. During the same period, 47 were created. However, the total number of laboratories has not increased since 11 laboratories became CNRS laboratories under the agreement signed with the latter organization which is discussed below. Both at INSERM and CNRS, it has become obvious that, if research is to remain competitive, it is necessary to have efficient teams and concentrate financial resources. This can only be achieved by maintaining the number of laboratories at the reasonable level and eliminating poor performers. In contrast with U.S. practices, researchers, may not be dismissed because they are protected by their civil service status and must therefore be reassigned.

Relations Between the Various Medical Research Institutions. Because there are so many institutions directly or indirectly engaged in medical research, areas of responsibility are not always clearly defined and interaction may be difficult. If CNRS and INSERM seem to be somewhat successful in their attempt to resolve this difficulty, such is not the case with the Pasteur Institutes. The problem is not as acute in other reserach institutions that are not involved in medical research to the same extent.

Relations Between CNRS and INSERM. For historical reasons, two major institutions that specialize in

medical research exist in France. INSERM was created because at that time, biology was not well developed at CNRS. In response, CNRS started to focus on life sciences. The CNRS Life Sciences Directorate was initially aimed at basic research while INSERM was supposed to conduct applied research. This distinction quickly blurred, resulting in the current situation where two institutions cover the same fields. This generates obvious problems but it can also be very dynamic in that both institutions can complement each other, not to mention that competition in itself has very positive aspects.

The question may arise about why the two institutions do not merge; a merger would be difficult. There would be career problems since promotions are quicker at INSERM than at CNRS; also, unions would oppose a merger attempt. In fact, the major problems exist more at the unit and researchers' level than betweem the institutions as a whole. Whether these problems are detrimental to French biomedical research depends on whether competition is deemed to be useful for performance. Furthermore, the existence of only one institution would simplify procedures for researchers but would allow them less flexibility in that the current organization permits the researcher to obtain research support from one institution if it may not be obtained from the other.

At the institute level, there have always been close connections between INSERM and the CNRTS Life Sciences Directorate. In the past, this led to creating mixed CNRS/INSERM research units. These units were run by both organizations. In fact, there was dual management, assessment, and supervision. The system became very bureaucratic and quickly became unmanageable since the two organizations did not coordinate their actions. It also became so opaque that only the laboratories knew whether they were mixing units. In 1981, when INSERM finally decided to make a systematic survey, it discovered that, one-third (88) of its units were mixed. Both CNRS and INSERM then decided to find more efficient ways to cooperate. One problem was that associated units did not exist at INSERM and to create them would have required the establishment of a specific framework. The concern of the CNRS Life Sciences Directorate was that since many of its leading teams were connected with INSERM, 80 percent of the CNRS Life Sciences researchers could have requested to be permanently transferred tin INSERM. If medical research were to be conducted solely by INSERM, this would have been a substantial loss for CNRS, since life sciences is one of its most important directorates. This may even, in the long term, have jeopardized its existence as such. On the other hand, INSERM would have been unable to absorb additional researchers unless it had reallocated funds reserved for recruiting young researchers.

A first agreement was signed in 1983, replaced by a second agreement in January 1988. The objective was to maintain the mobility of researchers between the CNRS Life Sciences Directorate and INSERM but at the same time to define clear channels of command. However, if the agreement resolves the problem for researchers, it does not resolve that of the ITA's (Ingenieurs, Techniciens, Administratifs-Engineers, Technical and Administrative Staff). The 1988 agreement provides for four types of units:

1. UMI (Unites Mixtes-Mixed Units) fall under both institutions and are the only mixed units that both institutions wanted to maintain. Each institution contributes 50 percent to the financing of each mixeed unit. There are 28 mixed units corresponding to large laboratories. The UMIs must not exceed 15 percent of the total number of research units at INSERM.
2. UDC (Unites a Developpement Concerte-Units with Coordinated Development) come under one institution and accept an important number of researchers from the other institution. Currently, there is one UDC at INSERM and none at CNRS. They must not exceed 5 percent of the total number of units at INSERM or CNRS.
3. UFE (UnitesFederees-Federated Units) group the interests of laboratories that are geographically close and that wish to work together. Currently, there are three UFEs that group about 10 laboratories, and there is no limit to the number of such units.
4. UAF (Unites Affiliees-Affiliated Units) are units affiliated with one institution and in which the other institution agrees to assign one or several researchers after having reviewed the evaluation made by the first institution. Currently, there are no UAFs. INSERM expects to have about one hundred UAFs by the emd of 1988; there is no limit to the number of such units. Totally, 1,238 CNRS employees (718 researchers and 520 ITAs) and 928 INSERM employees (491 researchers and 437 ITAs) are affected by the new convention.

In spite of these measures, there is still a concern within the CNRS Life Sciences Directorate that their researchers may wish to eventually permanently join INSERM. However, this concern may not be justified. Of 1,800 INSERM researchers, 221 work in CNRS laboratories; of 2,000 CNRS life sciences researchers, 300 work in INSERM laboratories. Considering that not all of the 3,000 CNRS researchers are covering medical research, it is likely that, on a percentage basis, there are more CNRS researchers in INSERM laboratories than the reverse, but there is no dramatic imbalance.

In certain research fields, INSERM and CNRS compete, in others, they complement each other. The CNRS Life Sciences Directorate does not conduct research in public health and epidemiology while INSERM does. On the other hand, INSERM

does not cover plant biology while CNRS does. CNRS can assist INSERM when connections are needed with engineering physics, the human and social sciences, and chemistry. If INSERM needs new materials for biological and medical engineering, they can turn to CNRS. The INSERM which is well established in CHUs brings that connection to CNRS.

The example of the CNRS INSERM AIDS program will illustrate that both INSERM and the CNRS Life Sciences Directorate can productively cooperate. This program includes:

1. Two subprograms on molecular virology and immunology that involve both basic and applied research. These are mixed subprograms and are run by and carried out in the laboratories of both INSERM and CNRS.
2. Two subprograms on pathology run by INSERM principally in CHUs.
3. One subprogram on therapeutic tests run by INSERM principally in CHUs.
4. One subprogram on epidemiology in Africa run by INSERM.

Therefore, INSERM and CNRS collaborate on AIDS research. The INSERM is solely responsible for the subprograms that are clearly medical.

Relations with the Pasteur Institutes. The Pasteur Institute in Paris numbers some 80 units, more than half of which are in some way associated with CNRS or INSERM (mixed units, external research contracts). In spite of this, medical public research institutions generally find it difficult to collaborate with the Institute which is often compared with a fortress. As a matter of fact, if there are CNRS and INSERM researchers on the campus of the Pasteur Institute in Paris (famous French AIDS researcher Luc Montagnier works on the premises of the Pasteur Institute but is in fact a CNRS researcher paid by CNRS) there are no Pastorian researchers outside of the institute. This is caused by a somewhat elitist Pastorian tradition but also by their industrial relations policy. It is true that both INSERM and CNRS are represented on the board of directors of the Pasteur Institute in Paris. In spite of this, there is not much coordination on scientific perspectives.

The situation is different with ORSTOM. The ORSTROM works with the overseas Pasteur Institutes which are privileged partners in medical research. The ORSTOM signed a general convention with the Pasteur Institute in Paris and specific agreements with the overseas Pasteur Institutes. In general, ORSTOM teams work in the Pasteur Institute's laboratories. In some cases, ORSTOM researchers head these laboratories; e.g., Daker and Yaounde. The ORSTOM and the overseas Pasteur Institutes are trying to complement each other rather than duplicate studies. For example, in Africa the overseas Pasteur Institutes conduct research in virology while ORSTOM specializes in epidemiology and transmission of diseases. Collaboration between ORSTOM and the overseas Pasteur Institutes seems to function well.

Relations with Other Public Research Institutions. The INSERM and CNRS signed agreements with ORSTOM. The agreement signed between INSERM and ORSTOM in June 1986 has not produced anything so far. The collaboration between ORSTOM and INSERM takes place principally within the framework of the North/South networks established by INSERM. These networks associate French laboratories and laboratories from developing countries that work together on themes of common interest; e.g., tropical diseases. Collaboration with CEA has taken the form of an UFE, located in the Nuclear Research Center of Grenoble, which federates four INSERM/CEA, two CNRS/CEA, and several CEA laboratories. The CEA also has joint programs and publications with the Curie Institute in radiobiology. The INSERM collaborates with another public research institution, INRIA (Institut National de Recherche en Informatique et Automatique- National Research Institute in Data Processing and Automation) to promote research on artificial intelligence. Collaboration between CNRS and INSERM with the Curie Institute is de facto since the latter's research units belong to the two organizations. Cooperation with INRA is on nutritional problems.

Public Financing. There are several sources and beneficiaries of public financing. Part of the funds received are then distributed to research units.

Sources of Public Financing. In France, approximately F10 billion ($1.67 billion) is spent on private and public health research. The government contributes about three-fourths of the funds to public medical research for reasons connected with the size of investments, the limited short-term profitability, the requirement for stable, regular and long-term financing, and the fact that medical research has a direct bearing on public health. Several ministries are involved in the funding process: the Ministry for Research which is the main source of financing, the Ministry of Health, the Ministry of Defense, and the Ministry of Cooperation. Subsidies are principally allocated to the major research institutions. In 1987, funds for biomedical research was F3.8 billion ($633 million) not including funds allocated to universities. The contribution of the Ministry for Research to university research is F1,410 million ($235 million) of which F350 million ($58.3 million) is allocated to life sciences. Since government support to universities is low, these largely rely on public research institutions for their financing.

The participation of local communities; e.g., departments, regions in the financing of public research remains limited although it has increased in the past few years (F4.1 million-$12.35 million in 1980; F246

million-$41 million in 1983). They usually intervene when their support contributes to the local economic development. Public health insurance organizations also participate in the public financing. In 1987, their contribution amounted to F40 million ($6.67 million). They usually only fund those research projects that will eventually lead to concrete applications in terms of the government also set up the FRT (Fonds de la Recherche et de la Technologie-Research and Technology Fund) whose purpose is to encourage technology transfer by giving financial incentives. The FRT was provided F930 million ($155 million) in 1988 of which F50 million ($8.3 million) has been allocated to the medical research program and F21 million ($3.5 million) to the biotechnology program. The new socialist government formed in June 1988 decided to allocate F500 million ($83.3 million) in additional funding to the FRT.

Beneficiaries of Public Financing. The INSERM and the CNRS Life Sciences Directorate are the primary beneficiaries of government subsidies. Since 1980, these have substantially increased. The INSERM budget went up from F956 million ($159.3 million) in 1981 to F1.6 billion ($266.7 million) in 1988, inclusive of salaries. The 1988 budget, exclusive of salaries, equals F520 million ($86.67 million), of which F335 million ($55.8 million) [64.5 percent of the budget exclusive of salaries, or 21 percent of the total budget] is for laboratory support, F49.6 million ($8.27 million) [9.5 percent of the budget exclusive of salaries, or 3.1 percent of the total budget] is for contracts (external research contracts, young teams' contracts, networks) and F135.4 million ($22.6 million) [26 percent of the budget, exclusive of salaries, or 8.5 percent of the total budget] is for administration and technology transfer. It is necessary to emphasize at this point that in all medical research institutions, and more generally in public research institutions, salaries absorb approximately 65 to 70 percent of the budget. Therefore, Institutions do not have wide latitude for independent action. Furthermore, any public measure to curtail budgets would necessarily affect research negatively since salaries cannot be reduced. The CNRS budget, exclusive of salaries, increased by a yearly average of 2.7 percent between 1983 and 1987. Inclusive of salaries, it amounts in 1988 to F9.89 billion ($1.65 billion). In 1985, it represented 21 percent of the French R&D budget. Of this amount, F6.9 billion ($1.15 billion) is allocated to the scientific directorates. The CNRS Life Sciences Directorate received F1.750 billion ($291.7 million) including salaries in 1988, that is 25.5 percent of the CNRS total budget, which is the highest budgetary allocation in comparison with the other directorates. Its budget, exclusive of salaries, equals F398 million ($66.33 million). The CNRS Life Sciences Directorate budget, exclusive of salaries, increased by an average of 4.5 percent in volume between 1983 and 1987, and came second after the Engineering Physics Directorate (5.8 percent) It is now stablizing and following the general progression of the CNRS budget. The increase in the life sciences budget is because the directorate has been considered as a priority in the past few years for two major reasons.

1. Research in life sciences uses rapidly changing and more and more costly techniques; e.g., genetic engineering, molecular biology.
2. The Life Sciences Directorate has focused on supporting the best laboratories rather than on creating new positions.

Because of this policy, it was in a strong position during budgetary negotiations. But again, because arbitration between the various directorates is necessary at CNRS, there is less budgetary flexibility than at INSERM. Also, considering that the CNRS Life Sciences Directorate does not only cover biomedical research, INSERM, whose entire budget is strictly for this research, has more financial resources to conduct research in that specific field. The INRA's budget for 1987 was F2.2 billion ($366.67 million) including salaries, and F500 million ($83.33 million), exclusive of salaries. The Directorate for Animal Production receives approximately one third of the budget. The Food and Nutrition Directorate received in 1987 approximately F200 million ($33.33 million), including salaries, and approximately F75 million ($12.5 million), exclusive of salaries.

The CEA budget for 1986 was F17.413 billion ($2.90 billion) including salaries. The 1986 budget for biomedical rexsearch; i.e., basic medical research, clinical medical research, research in radioprotection and radiopathology, biological, and genetic engineering equaled F201 million ($33.5 million), including salaries.

The ORSTOM budget equals approximately F800 million ($133.33 million), including salaries. The ORSTOM Health Directorate budget equals F5 million ($833,000), exclusive of salaries. The Health Directorate also receives numerous external contributions from host countries, interstate organizations, and international organizations. The distinguishing feature of all these public institutions is that they receive most of their funds (85 to 90 percent) from the government. The remaining 10 to 15 percent is derived from their own resources, such as contracts, license fees, and patents. The situation of semi-public institutions is very different in that respect since the governmental subsidy represents less than 50 percent of their budget. In 1987, the Pasteur Paris budget amounted to F500 million ($83.33 million) including salaries. Personnel costs represented 58 percent of that amount, which is less than in public institutions. This is because Pasteur houses many outside researchers paid by INSERM and CNRS, among others. Therefore, Pasteur Paris is

comparatively richer than public institutions. It has adopted a multi-financing system. It receives 47 percent of its budget from the government; 29 percent from its own resources (specialized production, R&D contracts, service laboratories, administration of its own estate); 14 percent from private financial sources (donations, legacies); 10 percent from industrial royalties through the two industrial affiliates of Pasteur Paris. The six overseas Pasteur institutes for which Pasteur Paris is administratively, financially, and technically responsible are subsidized by the Ministry of Cooperation and receive contracts from the World Health Organization. They do not receive any private financial support. The other overseas Pasteur Institutes are financed by the host country.

In 1988, the budget of the Curie Institute is approximately F400 million ($66.67 million), including salaries, of which F150 million ($25 million) is for research. The rest is for the hospital section. The Curie Institute receives approximately 64 percent of its total budget from cancer treatment, 20 percent from the government, 9 percent from private sources (donations and legacies), and 7 percent from research contracts. The research budget consists of the government subsidy, plus the funding received from private sources and research contracts. Therefore, the research budget represents approximately 36 percent of the total budget. In view of this, the government contribution to research is about 56 percent, private sources 25 percent, and research contracts 19 percent.

Financing of Research Units. Research units receive an annual global allocation from research institutions which each unit director distributes as he deems appropriate. This procedure, which used to be much more bureaucratic and cumbersome, was established by the law of July 15, 1982, for research and technological development, to give flexibility to the system and give unit directors who are in the best position to determine how to use funds, the responsibility for the proper distribution. In general, INSERM and CNRS contribute 70 percent of the financing of their own research units; i.e., units administered by INSERM or CNRS only and therefore exclusive of associate or mixed units, the remaining 30 percent is provided by other sources, whether public (contracts, subsidies) or private (non-profit organizations, private corporations). At INSERM, each year in August, a questionnaire is sent to research units asking them to give certain information relative to their research themes, their human and financial resources (both INSERM and other organizations), and budget estimates for the next fiscal year. In the past, certain data could not be verified by INSERM, but now the system is becoming more and more transparent. For instance, the amount of funds provided by other public institutions can now be verified. However, certain data still cannot be checked, mainly the contributions from non-profit organizations. The information submitted by research units is reviewed. Based on this analysis, INSERM determines how much money each unit will be allotted.

FOOTNOTES

1. Only INSERM and the Pasteur and Curie Institutes are medical research institutions. All other institutions, including CNRS, have directorates responsible for medical reaearch. However, for the purpose of this report, they all come under this heading.
2. The rate that will be used throughout this report is 1 dollar equals F6.

Italy

For further information on Italian items, contact Gerald Whitman, Office of Science Counselor, American Embassy, APO New York 09794-9500.

Polyester Research Cente Inaugurated in Southern Italy. The Italian company Montefibre inaugurated in Acerra (near Naples) is a research center for polyester and synthetic fibers. The center, with an investment of 7 billion lire (about $5 million), will employ 58 researchers, is equipped with a 6,000-volume technical library, and employs advanced techniques for high speed spinning. Research on polyester polymers will concentrate on fire resistant fibers and technopolymers for printing films for audio-visual devices and computers. The center will also develop new technologies for polyester recycling.

First Refrigerator Without CFC Presented. The Italian National Research Council's Institute for Freezing Technology presented the first non-CFC refrigerator in Italy employing tetrachloroethane (R134A) instead of dichlorodifluoromethane (R12). R134A is not hazardous to the ozone layer, but its performance is inferior to that of R12 and its level of toxicity has not yet been tested. The institute is also carrying out research on other substitutes for R12, such as dimethilether (DME) and cyclopropane.

Italian Senate Debates Creating Government Agency for Technological Innovation. During a recent hearing, the Italian Senate's Committee for Industry proposed the creation of a government agency for technological innovation. The agency would ease the transfer of research to industry, facilitate the awarding of funds to industry for innovation, and study special forms of tax exemption and public and private capital joint ventures. Among the speakers, the President of the National Agency for Nuclear and Renewable Energy favored the creation of the agency, while the Fiat representative expressed fears that the agency might become another bureaucratic impediment.

Italian Machine Tools Production and Sales Improve. In the first tri-

mester of 1989, the domestic sale of Italian machine tools increased 5.7 percent over the same period of 1988, while sales abroad increased 38.9 percent, especially to France, West Germany, U.S.S.R., and the U.S. In 1988, total business turnover of machine tools was 4,000 billion lire; 1,840 were sales abroad, an increase of 26 percent over 1987. The forecast for 1989 is for a total production of 4,800 billion lire with 2,300 billion in sales abroad.

New Biotech Company to Produce Human Skin. Cellife, a new Milan company, is creating a production center for human skin that will be able to produce from a fragment of healthy skin up to two square meters of new epithelium. Cellife will work in cooperation with schools of medicine in Italian universities that have centers for burns and plastic surgery. The company expects a business turnover of 5 million lire (about $3.5 million) after three years.

CISE Presents the First Superconductor Bearing. The Italian National Electricity Agency's research laboratory, CISE, has presented a model of a frictionless, high speed magnetic levitation bearing, which exploits the properties of superconductors. The bearing, made of YBCO (yttrium, barium, and copper oxides), is kept at minus 196 degree centigrade. In the model presented by CISE, a magnetic rotor uses two superconducting bearings cooled with liquid nitrogen. Possible applications for this device include precision mechanics, electronics, informatics, and the aerospace industry and medical industries.

FIAR in Advanced Space Cooperation with Soviet Union. The Milan company, FIAR, announced that it will cooperate with the Soviet agency Glavkosmos for manned flights, telecommunications and earth monitoring, and with Intercosmos for interplanetary exploration. FIAR will develop for the Soviet Mars exploration vehicle "Marshod" an advanced navigation system using artificial intelligence. For the Soviet solar studies program "Regata," FIAR will build a fleet of small probes (200 to 300 kilos) to be launched towards the sun. A FIAR official noted that the main obstacle to the realization of this program is COCOM authorization that might be difficult to obtain for the export of advanced technology to the U.S.S.R.

ASI Finances SAX and SAX X Satellites. The Italian Space Agency (ASI) is giving 40 billion lire (about $3 million) to Aeritalia for the construction of the SAX satellite scheduled to be launched in 1993. The SAX will study stellar X-ray radiation. The ASI is also providing 58 billion lire (about $4 million) to Selenia Spazio for construction of SAX X scheduled to be flown aboard the shuttle in 1991. The SAX X will perform magnetic remote sensing of the earth for application to studies on environment, oceanography, meteorology, and mapping.

Ferlini Sells Patent to U.S. General Atomic. The Genoa company, Ferlini, has tested and operated in Sardinia a patented apparatus for desulphurization of combustion gases. The plant is composed of four towers connected in series through which SO2, produced by industrial spent gases, is recycled into sulphuric acid and hydrogen. The process employs bromium which is continuously recycled through electrolysis. Ferlinisigned a contract with General Atomic of San Diego, California, to exploit the patent in North America where in 1990 a plant will be built that is 10 times bigger than the one operating in Sardinia.

West Germany

For further information on West Germany items, contact Mr. Edward M. Malloy, Science Counselor, American Embassy, Bonn, APO New York 09080-7400, Siemens AG, Hoechst AG.

West Germans Seek Alternative LRAACA Mission Avionics

West Germany is looking for an alternative to the U.S. mission avionics installed in its choice of maritime patrol aircraft to replace Navy Atlantic MK.1s. Germany has declared its intention to collaborate with the U.S. Navy in developing the long-range air-ASW-capable aircraft (LRAACA), but is seeking an alternative to the Boeing Update IV avionics planned for the Germany-based Orion P-3 aircraft. The U.S. Navy has said that development of the update IV avionics suite is too far advanced for any German involvement. Germany, through MPS-90 main contractor Dornier, wants to gain a slice of air vehicle and avionics development in return for buying LRAACA.

The German moves are being watched closely by other European NATO nations because the LRAACA air vehicle is now the leading candidate to replace the maritime patrol aircraft of other NATO nations. Germany appears to favor development of a European mission avionics suite as an alternative to Update IV. The German Navy's selection of LRAACA over France's assault-Breguet Atlantic ATL.2 (and improved ATL.3) has been approved by the German Ministry of Defense, although it has not passed a key meeting committing DM340 million ($195 million) for development and earmarking DM2-3 billion for procurement of an initial 12, (eventually 18) aircraft starting in 1996.

Lockheed won the LRAACA contest in October 1988, receiving an interim $250,000 engineering analysis contract. The U.S. Navy requires an initial 125 aircraft worth $3-5 billion. The LRAACA is virtually a new aircraft, retaining only the fuselage barrel in common with the P-3C. Changes include new engines, cockpit, avionics, flight controls, and materials.

Two prototypes will be built. Germany could provide up to 10 percent

of air vehicle development funds, with German companies being allowed to bid for work on the aircraft.

Italy has already requested LRAACA information from Lockheed and could follow with a request for proposals in late 1989, leading to a go ahead in 1990-91. The U.K. program is running about a year behind, and is most likely to involve the transplanting of existing Nimrod MR.2 mission avionics into the LRAACA air vehicle, followed by an avionics update in the late 1990s.

France is to slow down the already crawling Atlantique ATL.2 program to provide funds for developing the Rafale fighter. Observers believe that, having lost the key German contest, France could scrap the program.

CHANGE REQUEST
NAVEUR-ONR-5605/1 (Rev. 3-85)

FOR YOUR CONVENIENCE...

Government regulations require up-to-date distribution lists for all periodicals. This form is provided for your convenience to indicate changes or corrections. If a change in our mailing lists should be made, or if you want any of the ONREUR publications abstracted in this issue and listed below, please check the appropriate numbers. Fold on dotted lines, being sure our address is on the outside, tape or staple the lower edge together, and mail.

1. CHANGE OR CORRECT MY ADDRESS EFFECTIVE IMMEDIATELY OR (date)
2. DELETE MY NAME FROM DISTRIBUTION LIST
3. PLEASE SEND ME THE FOLLOWING ONREUR PUBLICATIONS

Corrected or New Address

__9-9-C __9-10-C __9-11-C __25-89
__26-89 __27-89 __28-89 __29-89
__30-89 __31-89 __32-89 __33-89
__34-89 __35-89 __36-89 __37-89
__38-89 __39-89 __40-89 __41-89

Fold Here

Fold Here

FROM:

_____

_____

_____

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE $300

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES

BUSINESS REPLY MAIL
FIRST CLASS PERMIT NO 12503 WASHINGTON DC

POSTAGE WILL BE PAID BY DEPARTMENT OF THE NAVY

Commanding Officer
Office of Naval Research European Office
Box 39
FPO New York 09510-0700

END

FILMED

9-89

DTIC